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# GESAMT HÄMOGLOBIN UND BLUTVOLUMEN DER RATTE NACH SUBLETHALER GANZKÖRPER RÖNTGENBESTRAHLUNG

von

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Zu den bekannten Folgen einer sublethalen Röntgenbestrahlung gehört das Auftreten einer Anämie. Der Grad dieser Anämie ist abhängig von der Höhe der Röntgendosis und je nach Tierspezies verschieden. Sowohl die Entwicklung der Anämie wie deren Rückbildung haben ein nicht unerhebliches praktisches und theoretisches Interesse. Am Grad der Anämie lassen sich Umfang eines Strahlenschadens, dessen sich abzeichnenden deletären Folgen oder auch die Wirksamkeit therapeutischer Massnahmen erkennen. Bei der hohen Strahlenempfindlichkeit der blutbildenden Gewebe sind aus der Hemmung der Blutbildung nicht nur allgemeine Rückschlüsse auf den qualitativen und quantitativen Effekt ionisierender Strahlen möglich, vielmehr wird so auch die Kinetik der Blutbildung selbst einer Analyse zugänglich.

Der Nachweis einer Anämie ist dann einfach, wenn bei unverändertem Blutvolumen nur die Zahl der Erythrozyten absinkt: es genügt, relative

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globin unter der Annahme eines Molekulargewichts von 68 000 für Hämoglobin und 650 für Hämin.

Das Blutvolumen wurde aus dem Gesamt Hämoglobin und der Hämoglobinkonzentration des Schwanzblutes × 0.75 berechnet (0.75 ist ein Umrechnungsfaktor für den Körperhämatokrit). Die Hämoglobinkonzentration von 0.025 ml Blut wurde spektrophotometrisch als Oxyhämoglobin bei einer Wellenlänge $\lambda = 545$ m$\mu$, der Hämatokrit mit Hilfe einer Mikromethode (International Hämacrit-Centrifuge) bestimmt. Für methodologische Einzelheiten s. TRIBUKAIT 1960b). Das Plasma- und Erythrozytenvolumen ergeben sich aus dem Gesamt Hämoglobin, der Hämoglobinkonzentration und dem Hämatokrit entsprechend

$$\text{tot. Pl. Vol.} = \frac{\text{tot. Hb} \times 100}{\text{rel Hb}} \times \frac{100-\text{Hct}}{100}$$

und

$$\text{tot. Ery. Vol.} = \frac{\text{tot. Hb} \times 100}{\text{rel. Hb}} \times \frac{\text{Hct}}{100}$$

Die Reticulozyten von 2 × 1 000 Erythrozyten wurden entsprechend der Methode von LARSSON & SWENSSON (1949) ausgezählt. Dabei werden dünne Blutausstriche in 1 iger Sublimatlösung fixiert und mit Toluidinblaulösung (0.75 %, pH 5.7) gefärbt.

Aufschluss über eine eventuell vorliegende Hämolyse erhält man aus dem vorzeitigen Abfall der Radioaktivität in vivo gezeichneten Hämoglobins bzw. Hämins. Wie zur Bestimmung der Erythrozytenlebenszeit (FORSSBERG & TRIBUKAIT 1962a) wurde den Tieren je etwa 10 $\mu$Ci (0.169 mg) C 2-Glycin i. p. injiziert. Etwa 0.2 bis 0.3 der injizierten Aktivität befindet sich im Hämin bis zum ca. 40. Tag nach der Injektion in etwa gleichbleibender Menge, wo der physiologische Erythrozytenabbau einsetzt und damit auch die Aktivität abfällt. Hämin wurde von etwa 0.1 bis 0.2 ml Schwanzblut nach der von FORSSBERG & TRIBUKAIT (1960b) beschriebenen Mikromethode isoliert. Das kristallinische Hämin wurde in 0.5 ml einer 0.02-n NaOH Lösung gelöst. 0.3 ml wurden auf einer Aluminiumplatte in einer unendlich dünnen Schicht luftgetrocknet und deren Aktivität bestimmt. Gleichzeitig wurde die Häminkonzentration von 0.1 ml der Lösung nach der Methode von PAUL, THEORELL & ÅKESON (1953) als Pyridinhämochromogen spektrophotometrisch gemessen. Daraus ergibt sich die spezifische Häminaktivität, zusammen mit dem Gesamt Hämin die gesamte Häminaktivität.

Die Röntgenbestrahlung wurde bei 230 kV, 15 mA und einer HWS = 0.5 mm Cu vorgenommen. Um eine möglichst homogene Durchstrahlung zu

Blutwerte (Hämoglobin Erythrozytenkonzentration Hämatokrit) zu bestimmen Ändert sich jedoch neben der Erythrozytenzahl auch das Blutvolumen führen relative Blutwerte zu einer falschen Einschätzung einer Anämie letzteres gilt für die Anämie gewisser Tiere nach Röntgenbestrahlung STOREY et coll (1950) fanden beim Kaninchen während der ersten 14 Tage nach einer subletalen Röntgenbestrahlung nicht nur ein Absinken des Erythrozytenvolumens, sondern auch des Plasmavolumens. Die relativen Blutwerte zeigten so trotz einer aufgehobenen Erythrozytenneubildung und eines grösseren Erythrozytenverlustes scheinbare Normalverhältnisse an Ähnliche Verhältnisse wurden von den gleichen Untersuchern auch bei der Maus und von GILBERT et coll (1962) beim Rhesusaffen gefunden Bei der Ratte, eines der für hämatologische Studien im Zusammenhang mit Röntgenbestrahlung meist verwendeten Tiere scheinen derartige Studien nicht vorzuliegen

Absicht der vorliegenden Arbeit ist einen Überblick über die Blutwerte und die Bildungs- und Abbauverhältnisse der Erythrozyten bzw des Hämoglobins der Ratte nach einer subletalen Röntgenbestrahlung zu erhalten Dazu wurden nach einer Bestrahlung mit 410 R Abfall und Wiederanstieg der relativen Blutwerte einschliesslich der Reticulozyten und der gesamten Hämoglobin bzw Erythrozytenmenge sowie das Verhalten des Blut und Plasmavolumens verfolgt Aus der gesamten Hämoglobinmenge und der Erythrozytenlebenslänge wurden ferner der Hämoglobinverlust bzw die Hämoglobinbildungsleistung während verschiedener Zeitabschnitte nach der Röntgenbestrahlung berechnet

*Material und Methodik* Die Untersuchungen wurden an männlichen Kragenratten eines Stammes ( hooded rats National Institute for Medical Research Mill Hill London) mit einem Ausgangsgewicht von etwa 300 g bei Versuchsbeginn vorgenommen Die Tiere erhielten ein speciellles Rattenbrot (Zusammensetzung s. TRIBUKAIT 1960a) sowie Hafer Mohrrüben und Wasser ad libitum

Die Gesamt Hämoglobinmenge wurde mit einer Modifikation der sogenannten alveolaren CO Methode bestimmt Dabei befindet sich das Tier solange in einem geschlossenen zirkulierenden Atemsystem dem etwas CO zugesetzt wird bis sich ein Gleichgewicht zwischen den Partialdrucken CO und $O_2$ der Atemluft einerseits und der COHb- und $O_2$Hb-Sättigung andererseits eingestellt hat Aus der Analyse der Atemgase bzw der vom Tier aufgenommenen CO Menge ergibt sich die Gesamtmenge Hämoglobin die so vom selben Tier beliebig oft und ohne Schaden bestimmt werden kann (TRIBUKAIT 1960b) Die Gesamtmenge Hämin berechnet sich aus dem Gesamt Hämo

globin unter der Annahme eines Molekulargewichts von 68 000 für Hämoglobin und 650 für Hämin

Das Blutvolumen wurde aus dem Gesamt Hämoglobin und der Hämoglobinkonzentration des Schwanzblutes × 0 75 berechnet (0 75 ist ein Umrechnungsfaktor für den Körperhämatokrit) Die Hämoglobinkonzentration von 0 025 ml Blut wurde spektrophotometrisch als Oxyhämoglobin bei einer Wellenlänge $\lambda = 545$ mμ der Hämatokrit mit Hilfe einer Mikromethode (International Hämacrit-Centrifuge) bestimmt. Für methodologische Einzelheiten s. TRIBUKAIT 1960b) Das Plasma und Erythrozytenvolumen ergeben sich aus dem Gesamt Hämoglobin, der Hämoglobinkonzentration und dem Hämatokrit entsprechend

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Die Röntgenbestrahlung wurde bei 250 kV 15 mA und einer HWS = 0.[illegible] mm Cu vorgenommen Um eine möglichst homogene Durchstrahlung zu

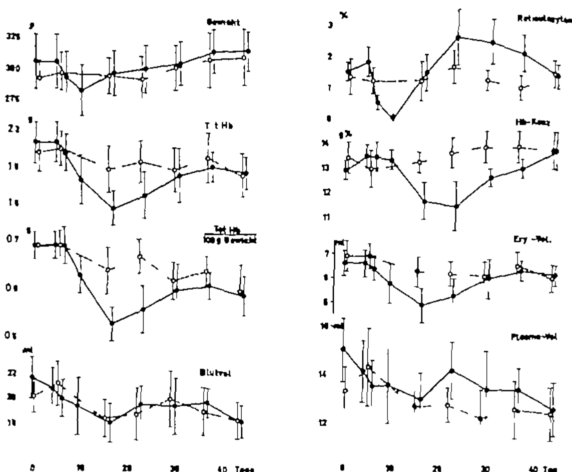



Abb. 1. Gewicht, Gesamthämoglobin, Gesamthämoglobin/100 g Körpergewicht, Blut-, Plasma- und Erythrozytenvolumen, Reticulozyten und Hämoglobinkonzentration von 10 Kontrolltieren (offene Symbole) und 9 röntgenbestrahlten Ratten (geschlossene Symbole). Mittelwerte mit Standardabweichung. Röntgenbestrahlung am Tag 5

erreichen wurde eine Gesamtdosis von 410 R mit einer Dosisgeschwindigkeit von 200 R/min in Einzeldosen jeweils von beiden Seiten und dorsal verabfolgt. *Die Ratten befanden sich bei der Bestrahlung in einem Pappbehälter und* waren nicht narkotisiert.

## Ergebnisse

Eine Übersicht der Veränderungen des Gewichts, des Gesamt-Hämoglobins, des Blut-, Plasma- und Erythrozytenvolumens sowie der relativen Blutwerte von 9 röntgenbestrahlten Tieren und 10 Kontrolltieren wird in Abb. 1 gezeigt.

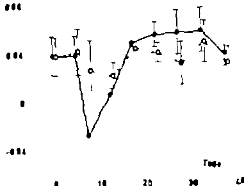



Abb. 2. Gebildete Hämoglobinmenge/Tag von 10 Kontrolltieren (offene Symbole) und 9 röntgenbestrahlten Ratten (geschlossene Symbole). Mittelwerte mit Standardabweichung. Röntgenbestrahlung am Tag 5

Das Körpergewicht sinkt innerhalb der ersten 4 Tage nach der Bestrahlung um etwa 8 % ($p < 0.001$), beginnt dann langsam anzusteigen und erreicht nach etwa 3 Wochen wieder sein Ausgangsgewicht.

Das Gesamt Hämoglobin fällt bis zum 11. Tag um etwa 25 % ($p < 0.001$) und steigt dann im Laufe der weiteren Beobachtungszeit von etwa 4 Wochen kontinuierlich, ohne jedoch ganz den Ausgangswert wieder zu erreichen. Berücksichtigt man jedoch, dass das Gesamt Hämoglobin von normalen Tieren mit zunehmendem Alter trotz steigendem Körpergewicht etwas abfällt (s. Kontrollen), entspricht der Endwert gänzlich dem zu erwartenden Normalwert. Das Erythrozytenvolumen entspricht dem Gesamt Hämoglobin weitgehend.

Das Blutvolumen ist, abgesehen von einem geringeren initialen Abfall, der aber auch bei den Kontrolltieren zu beobachten ist und somit nicht auf einer spezifischen Röntgenwirkung beruhen dürfte, im wesentlichen unverändert. Auf keinen Fall sinkt das Blutvolumen, eher mag um den 30. Tag nach der Röntgenbestrahlung eine Tendenz für etwas erhöhte Werte bestehen, statistisch zu sichernde Differenzen finden sich jedoch nicht.

Das im ganzen unveränderte Blutvolumen bedeutet, dass das Plasmavolumen entsprechend dem Abfall des Erythrozytenvolumens ansteigt und die Hämoglobinkonzentration den Änderungen des Gesamt Hämoglobins folgt. Der Hämatokrit läuft der Hämoglobinkonzentration parallel. Die Hämoglobinkonzentration der Erythrozyten, ausgedrückt durch das Verhältnis von Hämoglobinkonzentration × 100/Hämatokrit, ändert sich somit während der ganzen Versuchszeit nicht.

Die Reticulozyten des zirkulierenden Blutes sinken bereits 1 Tag nach der Bestrahlung von etwa 1.5 % auf 0.5 % ($p < 0.001$) und sind am 4. Tag

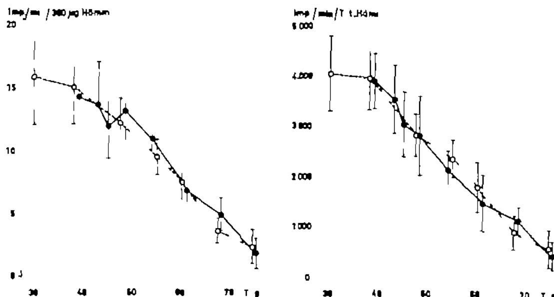



Abb. 3 Verhalten der spezifischen und gesamten Aktivität von in vivo mit C 2-Glycin radioaktiv gezeichnetem Hamin. Mittelwert mit Standardabweichung von 10 Kontrollierten (offene Symbole) und 9 röntgenbestrahlten Ratten (geschlossenen Symbole) Die Zeitskala der Abszissenachse bezieht sich auf den Tag der Injection von C 2 Glycin (Tag 0) Röntgenbestrahlung an Tag 44

praktisch aus dem Blut verschwunden Sie steigen dann aber an haben an 11 Tag wieder den Normalwert erreicht und liegen bis zum 31 Tag klar über den Werten der Kontrollen

Die Variationen und das Bildungsverhalten des Hämoglobins während der Phase des Abfalls und der der nachfolgenden Regeneration werden deutlicher wenn man deren tägliche Änderungen berechnet Die Resultate derartiger Berechnungen, wobei von den Gesamt Hämoglobinwerten und der für diesen Tierstamm gefundenen Erythrozytenlebenszeit von 55 Tagen (FORSSBERG & TRIBUKAIT 1962a) ausgegangen wurde, sind Abb 2 zu entnehmen Während der ersten 5 Tage nach der Bestrahlung sinkt die täglich gebildete Hämoglobinmenge von 0 04 g auf einen negativen Wert von — 0 03 g Das bedeutet dass nicht nur die Hämoglobinbildung vollständig gehemmt wird (in einem solchen Fall sinkt sie auf 0) sondern dass darüber hinaus der Organismus noch auf andere Weise Hämoglobin verliert Diese Menge ist jedoch absolut gesehen mit etwa 0 15 g = 7 % des Gesamthämoglobins relativ bescheiden Zwischen 6 und 10 Tag nach der Bestrahlung beträgt die Hämoglobinbildung etwa ± 0 Es lässt sich aus diesen Daten allein nicht entscheiden ob die Erythropoiese vollständig gehemmt wird oder ob ein etwaiger Hämoglobinverlust der Neubildung gerade die Waage hält. Zwischen dem 11 und 30 Tag kommt es zu einer positiven Bilanz, wobei die Hämoglobinbildung

klar über dem Niveau der Kontrollen bzw. dem Ausgangswert liegt, auf das sich die Hämoglobinbildung erst zwischen dem 30. und 35. Tag wieder ein stellt.

Das in Abb. 3 wiedergegebene Verhalten der spezifischen und gesamten Häminaktivität der röntgenbestrahlten Tiere unterscheidet sich nicht von dem der Kontrolltiere: bei beiden Tiergruppen beginnt die Aktivität etwa am 40. Tag nach Injektion des C-2-Glycin abzusinken, die beiden Kurven verläufe weisen eine weitgehende Parallelität zueinander auf. Daraus kann zwar der Schluss gezogen werden, dass die mittlere Lebenslänge dieser radioaktiv gezeichneten Erythrozytenfraktion unverändert ist. Jedoch muss offen bleiben, ob nicht der normale Abbaumechanismus physiologisch gealterter Erythrozyten gehemmt und durch einen anderen Abbaumechanismus ersetzt ist.

## Diskussion

An der Entwicklung der Anämie nach subletaler Röntgenbestrahlung sind zwei Prozesse beteiligt: (1) wird die Zellteilung gehemmt, womit bei der begrenzten Lebenslänge der Erythrozyten die gesamte Erythrozytenmenge absinkt; darüber hinaus werden (2) aber auch in verstärktem Umfang Erythrozyten abgebaut.

Vor allem Verteilungs- und Inkorporationsstudien der hämatopoetisch aktiven Gewebe und der Erythrozyten mit radioaktivem Eisen ($^{59}$Fe) haben zu einem klaren Bild des Umfangs und des zeitlichen Verlaufs der Hemmung der Erythropoese bei verschiedenen Bestrahlungsdosen geführt. Bei einer Röntgendosis von 400 R, wie sie auch hier verwendet wurde, wurde nach den Untersuchungen von LAMERTON, BELCHER & HARRISS (1959) die Eiseninkorporation in die Erythrozyten der Ratte innerhalb von 24 Stunden praktisch vollständig gehemmt und begann erst etwa 5 Tage nach der Bestrahlung wieder anzusteigen.

Für den gesteigerten Abbau der Erythrozyten nach einer Röntgenbestrahlung scheint der Permeabilitätssteigerung des Gefässystems entscheidende Bedeutung zuzukommen. Neben kleineren Blutungen vor allem in den Lymphknoten, verbunden mit einem Abbau von Erythrozyten in den Lymphknoten, treten nach den Untersuchungen u. a. von ROSS, FURTH & BIGELOW (1952) sowie STOHLMAN et coll. (1957) Erythrozyten in beträchtlichem Umfang aus dem Kreislauf in das Gewebe über und gelangen über das Lymphsystem wieder zurück in den Kreislauf. Bei dieser extravaskulären Wanderung scheinen die Erythrozyten so geschädigt zu werden, dass sie einem vorzeitigen Abbau anheimfallen. Eine direkte Röntgenschädigung der Erythrozyten dürfte nicht

vorzuliegen nach SHEETS et coll (1954) beeinflusst eine in vitro-Bestrahlung von Erythrozyten mit 2 000 R deren Lebenslänge nicht

Die vorliegenden Versuchsresultate lassen sich gut mit den genannten Vorstellungen über die Entwicklung der Anämie nach einer Röntgenbestrahlung in Einklang bringen. Sie geben gleichzeitig ein Bild über den zeitlichen Ablauf der Hemmung bzw des Anstiegs der Zellbildung und des erhöhten Abbaus der Erythrozyten Darüber hinaus wird die komplexe Natur vor allem des gesteigerten Zellabbaus deutlich

Die Zellbildung ist wie sich aus den Reticulozytenwerten erkennen lässt einen Tag nach der Röntgenbestrahlung weitgehend und vier Tage nach der Röntgenbestrahlung vollständig gehemmt In Übereinstimmung mit den Ergebnissen von LAMERTON BELCHER & HARRISS (1959) setzt bei der Ratte nach einer Bestrahlungsdosis von etwa 400 R um den 5 Tag herum die Zellneubildung ein Zu diesem Zeitpunkt fällt die gesamte Hämoglobinmenge in zunehmendem Masse und erreicht um den 11 Tag trotz normaler Reticulozytenwerte, d h einer normalen Zellbildungsleistung ein Minimum Es lässt sich daraus auf einen erhöhten Zellabbau — in der Grössenordnung von etwa dem Doppelten der Norm — schliessen Der zeitliche Verlauf des gesteigerten Erythrozytenabbaus stimmt mit anderen Untersuchungen überein Ross FURTH & BIGELOW (1952) fanden bei der mit 750 R bestrahlten Ratte zwischen dem 7 und 14 Tag nach der Bestrahlung ein Maximum an Erythrozyten in der Lymphe Bei dem mit 700 bis 1 000 R bestrahltem Kaninchen sind die Verhältnisse ähnlich (KAHN & FURTH 1952) Es sei hier noch besonders darauf hingewiesen dass zum Zeitpunkt dieses gesteigerten Erythrozytenabbaus nicht nur die Zellregeneration wieder eingesetzt sondern sich auch das Allgemeinbefinden der Tiere deutlich verbessert hat die Tiere fressen wieder normal und steigern ihr Gewicht nach einer Periode von Fressunlust und Gewichtsabfall

Die Hämoglobinbildungsleistung der Ratte bei der Anämie nach Röntgenbestrahlung ist im Vergleich zur Hämoglobinbildung bei der Blutungsanämie wesentlich geringer Bei einer durch Blutung hervorgerufenen Anämie von etwa gleichem Umfang wie die hier beschriebene Bestrahlungsanämie ist die Hämoglobinbildung etwa verdoppelt (TRIBUKAIT 1960c) hier weniger als 50 höher als normal Das dürfte weitgehend auf der Schädigung des erythropoietischen Gewebes beruhen Als Folge dieser reduzierten Hämoglobinbildungsleistung ist die Regenerationszeit bis zum Erreichen des Ausgangswertes gegenüber der Blutungsanämie etwa verdoppelt

Das Blutvolumen ist in den vorliegenden Untersuchungen im wesentlichen unverändert Trotz der kräftigen Steigerung der Permeabilität des Gefässystems wie sie aus dem Erythrozytenschwund aber auch dem Verhalten radio-

aktiv gezeichneten Plasmas, Evans blue u. a. nach Injektion in das Zirkulationssystem hervorgeht (s. beispielsweise FURTH et coll 1951) scheint die Blutvolumenregulation ungestört zu sein.

Der Erythrozytenabbau geht unter normalen Bedingungen bei der Ratte zu etwa 10 % in der Leber 60 % in der Milz, 10 % im Knochenmark und etwa 20 % in den übrigen Organen vor sich (HUGHES, JONES & CHESLEY 1961) Wo bei der röntgenbestrahlten Ratte die physiologisch gealterten Erythrozyten abgebaut werden und wo der zusätzliche Erythrozytenabbau geschieht, ist unbekannt. Da Knochenmark und Milz durch Röntgenbestrahlung stark beeinflusst werden, ist es möglich, dass damit verbunden auch der Erythrozytenabbau in diesen Organen verändert wird. Allerdings wird bei der Maus nach FURTH et coll. (1951) das Vermögen des Reticulo-Endothels, auch das der Milz, colloidales Gold aufzunehmen durch eine Röntgenbestrahlung nicht beeinflusst. Um eine Auffassung darüber zu erhalten ob der Abbau der physiologisch gealterten Erythrozyten normal abläuft wurden in den vorliegenden Untersuchungen die Ratten gerade zu dem Zeitpunkt röntgenbestrahlt, zu dem die zuvor radioaktiv gezeichneten Erythrozyten normalerweise aus den Blutkreislauf zu verschwinden beginnen. Aus einem verzögerten Abfall der Aktivität kann auf eine gestörte Funktion des erythrozyten-abbauenden Gewebes geschlossen werden. Umgekehrt kann aus einem rascheren Abfall der Aktivität unter Berücksichtigung der Veränderungen der gesamten Erythrozytenmenge und der Zellneubildung auf einen gesteigerten Abbau gerade der ältesten im Blute zirkulierenden Erythrozyten geschlossen werden. Der gefundene Abfall der radioaktiv gezeichneten Erythrozyten war für röntgenbestrahlte Tiere und Kontrollen gleich. Ein normaler Abbau der physiologisch gealterten Erythrozyten mag somit am wahrscheinlichsten erscheinen, obwohl nicht mit Sicherheit auszuschliessen ist, dass der Abbau an normaler Stelle (Leber Milz, Knochenmark) gehemmt ist und durch einen gerade entsprechenden Abbau in anderen Geweben ausgeglichen wird. Die Befunde sprechen weiter dafür dass bei dem gesteigerten Erythrozytenabbau nach einer Bestrahlung nicht bevorzugt physiologisch alte Erythrozyten zugrundegehen.

Die Untersuchungen wurden mit finanzieller Unterstützung durch „Statens Råd for Atomforskning" ausgeführt.

## ZUSAMMENFASSUNG

Nach Röntgenbestrahlung mit 410 R sinkt Gesamt Hämoglobin bzw. Erythrozytenvolumen der Ratte innerhalb von 11 Tagen kontinuierlich um etwa 25 % 6 Wochen nach Bestrahlung werden Normalwerte erreicht. Das Blutvolumen bleibt konstant. Keine Zell-

*bildung findet zwischen dem 1 bis 4 Tage statt setzt aber um den 6 Tag wieder ein* und ist bis zur Normalisierung des Gesamt Hämoglobins etwa verdoppelt Der tägliche Hämoglobinverlust ist während der ersten 14 Tage 2 bis 3-fach höher als normal Physiologisch alte Erythrozyten werden dabei gegenüber jungen nicht bevorzugt abgebaut.


## SUMMARY

On exposure of rats to 410 R roentgen rays, a continuous decrease in the total haemoglobin and erythrocyte volumes takes place and on the 11th day reaches 75 of the normal. After 6 weeks, however normal values are again attained The blood volume remains constant Cell division is completely blocked between the 1st and 4th days, but starts again at day 6, and is doubled at the stage when the total haemoglobin has reached a normal level The daily loss of haemoglobin is twice or 3 times the normal during the first two weeks. Physiologically old and young erythrocytes are decomposed at the same rate.

## RÉSUMÉ

Chez des rats exposés à 410 r de rayons röntgen on note une baisse continue de l'hémoglobine totale et du volume érythrocytaire jusqu à 75 de la normale au bout de 11 jours, avec retour à la normale au bout de 6 semaines. Le volume sanguin reste constant. La division cellulaire est complètement arrêtée du premier au quatrième jour mais repart au sixième et a doublé au moment ou l'hémoglobine totale a rejoint sa valeur normale Pendant les deux premières semaines, la perte quotidienne d hémoglobine est double ou triple de la normale. Les érythrocytes physiologiquement jeunes ou âgés sont détruits dans la même proportion.


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bildung findet zwischen dem 1 bis 4 Tage statt setzt aber um den 6 Tag wieder ein und ist bis zur Normalisierung des Gesamt Hämoglobins etwa verdoppelt. Der tägliche Hämoglobinverlust ist während der ersten 14 Tage 2 bis 3-fach höher als normal. Physiologisch alte Erythrozyten werden dabei gegenüber jungen nicht bevorzugt abgebaut

## SUMMARY

On exposure of rats to 410 R roentgen rays, a continuous decrease in the total haemoglobin and erythrocyte volumes takes place and on the *11*th day reaches 75 of the normal After 6 weeks, however normal values are again attained. The blood volume remains constant Cell division is completely blocked between the 1st and 4th days, but starts again at day 6, and is doubled at the stage when the total haemoglobin has reached a normal level The daily loss of haemoglobin is twice or 3 times the normal during the first two weeks. Physiologically old and young erythrocytes are decomposed at the same rate.

## RÉSUMÉ

Chez des rats exposés à 410 r de rayons röntgen on note une baisse continue de l'hémoglobine totale et du volume érythrocytaire jusqu à 75 de la normale au bout de 11 jours, avec retour à la normale au bout de 6 semaines. Le volume sanguin reste constant. La division cellulaire est complètement arrêtée du premier au quatrième jour mais repart au sixième et a doublé au moment ou l hémoglobine totale a rejoint sa valeur normale. Pendant les deux premières semaines, la perte quotidienne d'hémoglobine est double ou triple de la normale. Les érythrocytes physiologiquement jeunes ou âgés sont détruits dans la même proportion

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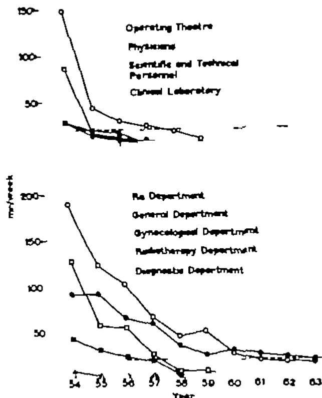



Fig 1 Average weekly exposure for different groups during the period 1954—1963. The trend is definite reduction with time, resulting from better radiation hygiene. The sensitivity of the PM 1 film is rather low for gamma rays, and doses less than 20 mr can hardly be measured. The values under the dotted line (20 mr) could be as high as this, except in the roentgen departments where the limit should be as low as 5 mr

radium department were the main problem in health physics, as may be recognized from a study of Fig 1 The average exposure of the staff in 1954 amounted to 190 mr/week, and the nurses received more than 200 mr/week.

The introduction of remote handling of the moulds, and a generally improved technique for the handling of appliances considerably reduced the exposure to the personnel in the radium department already during the first year The improved radiation hygiene moreover resulted in a significant reduction of exposure to staff in the other departments.

The distribution of the radiation load over the entire staff is shown in Fig 2 in which the percentages of personnel exposed to certain doses are given.

FROM THE NORWEGIAN RADIUM HOSPITAL, MONTEBELLO NORWAY

# REDUCTION OF PERSONNEL EXPOSURE IN THE NORWEGIAN RADIUM HOSPITAL 1954—1963

by

PER GRANDE and RAGNAR JAHREN

The Norwegian Radium Hospital has more than three hundred beds and treats only malignant disease Norsk Hydro s Institute for Cancer Research is an associated research centre

The radiation sources most commonly used during the period 1954—1963 were 10 to 250 kV roentgen units, one betatron with maximum energy of 31 MeV one 50 curie Cs unit radium for interstitial moulds and gynecologic treatment and radioactive isotopes mainly I and Au

A full time protection physicist was appointed in 1954 and a film service was started in August of the same year The radiation exposure to personnel, now presented refers to the results of the work in health physics

The energy distribution of the radiation being known a simple film badge with only one filter is used for differentiating between soft and hard radiation Ilford PM 1 is used as the monitoring film

The old French radium moulds for the treatment of carcinoma mammae were still in extensive use at the hospital in 1954 The working conditions in the

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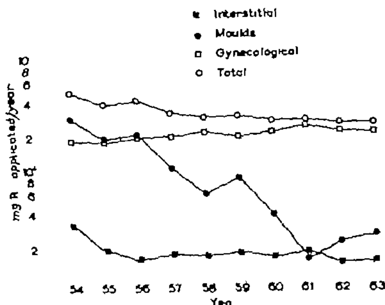



Fig. 3 Radium in milligrams, used yearly for interstitial moulds and gynecologic treatments in the period 1954—1963. The gynecologic use of radium slightly increased while that of radium for moulds decreased during the same period. The total amount of radium employed has decreased by factor of approximately 2 from 1954 to 1963.

and skill would justify the change. The falling trend of the exposure curve for the staff of the radium department (Fig 1) indicates that this assumption was correct It now seems that the exposure doses in the radium and gynecologic departments have reached a level where further reduction would necessitate a radical improvement in the working conditions.

The gynecologic ward patients stay with implanted radium in relatively small rooms for approximately 3 days so that the nursing staff is subjected to quit intense radiation. The planning of hospital wards where radiation therapy is to be administered by sources on or implanted in patients should ensure that th rooms are large enough for the purpose.

## SUMMARY

Exposure curves for the personnel at the Norwegian Radium Hospital for the period 1954—1963 are presented The progressive improvement in radiation hygiene and the means by which was attained, are discussed.

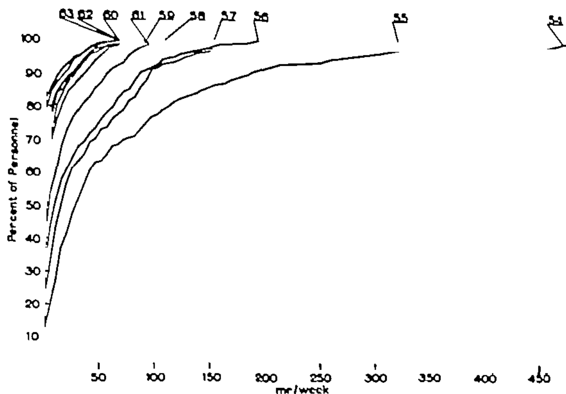



Fig. [illegible] Percentage of staff exposure for the period 1954—1963. The curves indicate the percentage of personnel exposed to a certain dose or less (cumulative distribution). In 1954 3[illegible] of the personnel received more than 50 mr/week, in 1963 only 2[illegible] were exposed to more than 50 mr/week.

The amount of radium (mg) used for interstitial moulds and gynecology is evident from Fig. 3. This also reveals that the employment of moulds has decreased with time and a comparison with Fig. 1 indicates that the reduction of the exposure of the personnel has followed the same trend. The total use of radium was reduced by a factor of approximately 2 during the whole period 1954—1963. The radiation exposure of the heaviest exposed group decreased however by almost one order of magnitude.

The hospital was moved in 1957 to a new building with more space and better working facilities with consequent further exposure reduction (Fig. 1).

As the use of moulds decreased it meant less work for the radium department. More effective employment of this group was obtained by reorganizing the gynecologic use of radium. This work was formerly carried out in the operating theatre but was transferred to the radium department in 1959. The staff of this department, being most experienced in the handling of radium applicators, would thus be of great help to the gynecologists and it was hoped that its care

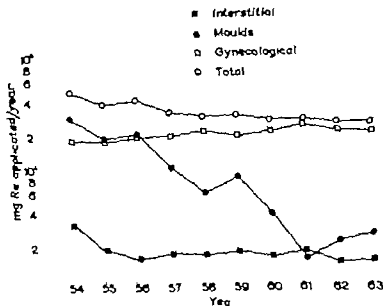



Fig. 3. Radium in milligrams, used yearly for interstitial, moulds and gynecologic treatments in the period 1954—1963. The gynecologic use of radium slightly increased, while that of radium for moulds decreased during the same period. The total amount of radium employed has decreased by a factor of approximately 2 from 1954 to 1963.

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The gynecologic ward patients stay with implanted radium in relatively small rooms for approximately 5 days so that the nursing staff is subjected to quite intense radiation. The planning of hospital wards where radiation therapy is to be administered by sources on or implanted in patients should ensure that the rooms are large enough for the purpose.

## SUMMARY

Exposure curves for the personnel at the Norwegian Radium Hospital for the period 1954 — 1963 are presented. The program of improvement in radiation hygiene and the means by which it was attained, are discussed.

## ZUSAMMENFASSUNG

Die Expositionskurven für das Personal des Norwegischen Radium Hospitals für die Periode 1954—1963 werden unterbreitet. Der Fortschritt in der Strahlenhygiene und die Massnahmen, die hierzu führten werden besprochen.

## RÉSUMÉ

Les auteurs présentent les courbes d'exposition aux radiations du personnel de l'Hôpital du Radium Norvégien pour la période 1954—1963. Ils étudient les améliorations progressives de la protection contre les radiations et les moyens qui y ont conduit.

FROM THE EDWARD MALLINCKRODT INSTITUTE OF RADIOLOGY (DIRECTOR HUGH M WILSON) AND THE DEPARTMENT OF ANATOMY (DIRECTOR EDWARD W DEMPSEY) WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, ST LOUIS, MISSOURI, U S. A.

# ANGIOGRAPHY OF THREE MALIGNANT TUMORS TRANSPLANTED INTO YOUNG MIDDLE-AGED AND OLD MICE

by

WILLIAM H McALISTER, ALEXANDER R MARGULIS and VALENTINA SUNTZEFF

The purpose of this paper is to compare the growth rates and vascularity as seen by angiography in three transplanted malignant tumors in young, middle aged, and old host mice.

*Material and Methods* Three age groups of mice (young middle-aged and old) served as hosts for transplanted rhabdomyosarcoma, lymphosarcoma, and hepatoma. A total of 145 C3H (Jackson Memorial Laboratory) and strain 129 Washington University School of Medicine) mice were used for this purpose.

*Rhabdomyosarcoma* This tumor was originally obtained in 1950 from Dr Elizabeth U Green s Laboratory in its seventieth transplant generation The tumor was first induced by the intramuscular injection of 0.5 mg of 20-methy cholanthrene suspended in filtered lard. The tumor appeared 71 days after the injection of carcinogen and was transplanted 24 days thereafter The recipient strain was C3H but was later changed to (C3H × DBA) F1 hybrids. The C3H

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**Table**

| Tumor type | Host mouse strain | Definition of age of host (months) | | | Number of host | | |
|---|---|---|---|---|---|---|---|
| | | Young | Middle-aged | Old | Young | Middle-aged | Old |
| Lymphosarcoma | C3H | 3 | 9 | 16 | 21 | 17 | 18 |
| Hepatoma | 129L | 3 | 1 —15 | 21—25 | 12 | 16 | 9 |
| Rhabdomyosarcoma | C3H | 3 | 9 | 16 | 18 | 11 | 23 |

mice which were to receive tumor transplants were shaved in our laboratories and the area was disinfected with 70 % alcohol The tumor to be implanted was excised cut into small pieces, washed in isotonic saline containing 50 ° streptomycin and 25 % penicillin and transplanted subcutaneously to the recipient animal by trocar After 6 to 7 days the transplanted tumor was easily palpated under the skin

The mice in group I (young) were 3 months those in group II (middle-aged) 9 months old and those of group III (old) 16 months old A 100 % growth of the tumor transplant was obtained in all three groups Radiologic observations were made three weeks after transplantation

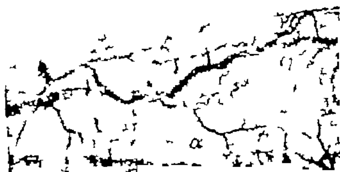
*Lymphosarcoma.* This tumor was also carried in C3H mice. It grew extremely fast, especially in young mice The tumor however was characterized by such diffuse growth in the subcutaneous tissue of the host that its accurate measurement was difficult Transplantation was accomplished as described for rhabdomyosarcoma, except that antibiotics were not used The tumor bearing mice were in identical age groups as those bearing rhabdomyosarcoma

*Hepatoma 129L* This tumor arose spontaneously in an old male mouse of strain No 129 in May 1957 and was transplanted to mice of the strain by the procedure described for lymphosarcoma Since that time the continuance of this tumor has been maintained in Wernse Laboratory of Washington University School of Medicine

The growth of hepatoma No 129L was extremely slow Microscopically it greatly resembles normal liver cells but the pattern of the liver is completely lost and numerous mitoses are observed Since mice of strain No 129 live longer than C3H mice, those of the following age groups were used I (young) were 3 months, II (middle aged) were 12 to 15 months, and III (old) were 21 to 25 months old The tumor take was 90 %

Angiography was performed when the tumors were approximately 1 to 1 5 cm in size Thorotrast was injected into the left ventricle of the heart via a





b



Fig. 1. Lymphosarcoma. ) Young host. b) Middle-aged host. Some diminution of vascularity ) Old host. Further decrease in number and size of vessels in tumor nd its bed.

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Angiography was performed when the tumors were approximately 1 to 1.5 cm in size. Thorotrast was injected into the left ventricle of the heart via a





b



Fig. 3. Rhabdomyosarcoma. a) Young host. A highly vascular tumor with multiple "lakes" or collections of contrast material. b. Middle-aged host. Slight decrease in vascularity. c) Old host. Definite decrease in vascularity including "lakes".

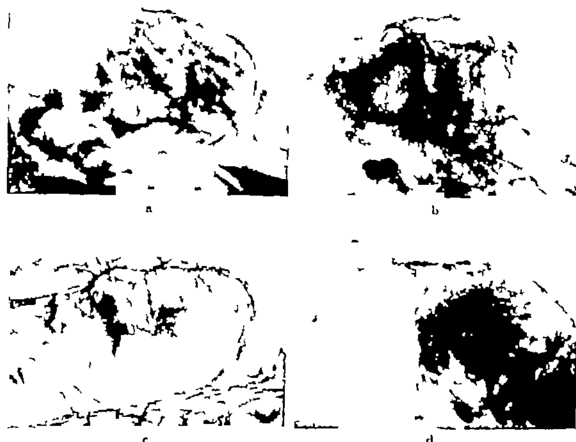


Fig 2 Hepatomas. ) Young host. b) Middle ged host Decrease in number of vessels i tumor nd its bed. ) Old host Further decrease in vascularity d) M ddle-aged host O lobule more vascular tha th other

catheter as previously reported (MARGULIS et coll 1961) Serial radiographic exposures were made during the filling of the vascular system The angiograms of the tumor and its bed were then enlarged ten times photographically

The angiograms were studied for appearances, abundance, and distribution of the vessels in the tumor and its bed The relative numbers of large and small vessels were compared and individual vessels were studied for tapering tortuosity and abrupt endings The collections and amount of con trast medium (lakes) were recorded The tumor type strain age and number of host mice are given in the Table on p 18

## Results

Growth of lymphosarcoma was fastest and that of hepatoma slowest The growth rate of lymphosarcoma was found to be higher in the younger than in the older host mice Tumor growth of rhabdomyosarcoma varied greatly

## ZUSAMMENFASSUNG

Transplantierte Lymphosarkome, Hepatome und Rhabdomyosarkome wurden auf junge, ältere und alte Mäuse eingepflanzt und studiert. Die Wachstumsschnelligkeit von Lymphosarkomen war deutlich geringer in alten Mäusen und wenigstens etwas geringer in mittelalten Mäusen; Hepatome wuchsen nicht gut in alten Mäusen. I Rhabdomyosarkomen wurde kein Unterschied nach Altersgruppen festgestellt. Es fand sich eine geringere Vaskularisation in den Lymphosarkomen und Hepatomen der alten Mäuse, aber weniger ausgesprochen in den Rhabdomyosarkomen.

## RÉSUMÉ

Les auteurs ont étudié des lymphosarcomes, des hépatomes et des rhabdomyosarcomes transplantés sur des souris jeunes, adultes et âgées. La croissance des lymphosarcomes est nettement ralentie chez les souris agées, et, à un moindre degré, chez les souris adultes. Les hépatomes croissent moins bien chez les souris âgées. Pour les rhabdomyosarcomes, la vitesse d'accroissement est la même dans les trois groupes d'âge. La vascularité des tumeurs est diminuée chez les souris âgées dans les lymphosarcomes et les hépatomes, mais moins dans les rhabdomyosarcomes.

## REFERENCES

MA[illegible]LLIS A. R., CARLSSON E., and MCALISTER W. H. Angiography of malignant tumors in mice. Acta radiol. 56 (1961) 179

but little difference in the average growth rate of the tumor was noted in the three age groups

Hepatoma transplants did not grow as well in old mice but the rate of growth in age groups I (young) and II (middle-aged) was similar No indication of growth of the tumor in group III can be given with certainty because some of the mice died of old age before the tumor was large enough for use, but the growth rate appeared slower in old mice

The vascularity was *found to have decreased in all three tumors and their* beds in old host mice (Figs 1c 2c, and 3c) These findings were most striking in lymphosarcoma, less marked in hepatoma, and were present to a lesser degree in rhabdomyosarcoma The character of the changes was similar in all three tumors in old mice but differed in degree and incidence The most frequent finding was a decrease in the number and size of large and small arteries and veins, as well as of unidentifiable small vessels. Tortuosity of arteries and veins was increased in tumors in old host mice but this finding was largely confined to hepatoma Laking' was present but much less frequent in *rhabdomyosarcoma and hepatoma in old host mice than when the same two* tumors grew in young mice The tumor bed vessels were decreased in old mice and closely paralleled the abundance and size of the vessels in the tumors. Again the changes were most striking in lymphosarcoma

Tumors of young mice had vascular appearances as previously described (MARGULIS et coll 1961) Typical patterns in the three tumors in the young host age group are illustrated in Figs 1a, 2a and 3a

The vascular patterns of the three tumors in middle-aged mice were some what unpredictable (Figs 1b 2b and 3b) In some tumors, especially in lymphosarcoma the vascular anatomy was similar to that encountered in old mice. Other tumors in regard to vascularity were indistinguishable from those seen in young hosts

Decrease in abundance and size of vessels in the hepatomas transplanted into middle aged hosts was less than that observed in the same tumor growing in old mice both in degree and incidence ( Fig 2 b and c) In a few hepatomas in middle-aged mice the vascular appearance of some lobules were similar to the features encountered in young hosts, whereas vascularity in other lobules in the same tumor was only scant (Fig 2d)

## SUMMARY

Transplanted lymphosarcoma, hepatoma, and rhabdomyosarcoma were studied in young middle-aged and old host mice. Th growth rates of lymphosarcoma were definitely decreased in the old mice and to a lesser degree in middle-aged mice. Hepatomas did not grow as well in old mice. In rhabdomyosarcoma the rate of tumor growth did not differ in th three age groups. The vascularity of the tumor decreased n the lymphosarcomas and hepatomas of old mice hosts, to a lesser degree in rhabdomyosarcomas.

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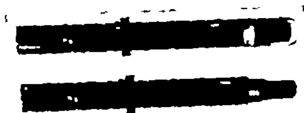


Fig. 1. Reference condenser chamber unit with and without cap, and with the shielded ring slid onto the stem.

chamber equipment. International comparisons from the period between 1953 to 1956 have shown that the original Swedish free-air standard chamber is still correct and stable within the measuring accuracy of such units.

The number of kilocurie gamma radiation therapy units was rather small in Sweden before 1960 and the dosemeters required for their operation were calibrated in the standard laboratories of the Institute of Radiophysics (RI). However the number of such units is now rapidly increasing and consequently also the number of dosemeters requiring calibration. It is usually rather inconvenient for the hospital physicists and for the RI standard laboratories to bring all these instruments to the RI for calibration. An alternative and more practical solution was therefore suggested in 1961.

The object in view was to provide an easily accessible reference instrument for gamma radiation exposure measurements in the radiotherapy clinics. The simplest answer to this demand seemed to be a reliably functioning condenser chamber dosemeter which could be calibrated and periodically checked by the RI standard laboratories by means of a specified and easily reproducible calibration technique. The dosemeter should be sturdy and easily transportable to the radiation therapy clinics in Sweden thereby enabling the hospital physicists to calibrate their dosemeters and thus to achieve the desired uniformity in clinical gamma radiation exposure measurements.

The condenser chamber was considered to be the most suitable type of dosemeter for the purpose, particularly because it is uncomplicated in design and fairly inexpensive. It can be operated by a hospital physicist alone, or even by an experienced technical assistant. The only instrumental equipment needed is an adequate electrometer carefully calibrated. It has been found from the many inspections of roentgen therapy installations in Sweden that a reliable condenser chamber competently used, gives sufficient accuracy in measurements of radiation exposure in clinical work.

The reference condenser chamber is shown in Fig. 1. There is a short external thread at the base of the thimble for attachment of the cap that is required for

FROM THE INSTITUTE OF RADIOPHYSICS (DIRECTOR PROF R. SIEVERT) KAROLINSKA SJUKHUSET STOCKHOLM SWEDEN

# NORMALIZATION OF CLINICAL GAMMA RADIATION EXPOSURE MEASUREMENTS IN SWEDEN

by

R THORAEUS

Instances of considerable errors in gamma radiation measurements with uncalibrated commercial dosemeters were reported in a recent paper (THORAEUS 1963) With that experience in mind and since correct measurement of the radiation is of fundamental importance in radiotherapy and in clinical radiophysics work it was considered necessary that a special national gamma radiation standard laboratory should be arranged similar to the roentgen radiation standard laboratory that was installed early in the 1930s (THORAEUS 1932 1963) The new gamma standard laboratory and its equipment the gamma radiation sources at disposal and some measurement results were described in the first mentioned paper

The system of periodical inspection of the roentgen therapy installations in Sweden and the experience gained have been described by SIEVERT (1925) and THORAEUS (1950) The radiation measurements carried out during these inspections are since the beginning of the 1930s based on calibrations in the above mentioned roentgen standard laboratory and its free air standard

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Table 2

*Change of response with length of irradiated portion of the stem*

| Length in cm of irradiated portion of stem measured from top of capped thimble | Type of radiation used | |
|---|---|---|
| | 250 kV roentgen | $^{60}Co$ gamma |
| 2 | 1.00 | 1.00 |
| 4 | 1.01 | 1.00 |
| 6 | 1.003 | 1.00 |
| 8 | 1.01 | 1.00 |
| 12 | 1.015 | 1.018 |
| 16 (full length) | 1.03 | 1.028 |

radiation from a 50 mCi radium source, using various exposure times and a constant geometry (THORAEUS 1956). The results obtained are given in Table 1. The percentage reduction of the potential per minute exposure does not indicate any tendency to systematic variation. It is recommended however that the loss in potential should be at least 100 volt and not more than 200 volt when a charging potential of 400 volt is used. This means a loss in potential of 25 to 50 %. This function study was later repeated at 5 times higher exposure rates, and the previously obtained results were confirmed.

With the same experimental conditions as for the recordings in Table 1 a 45 min exposure was used for checking stability. A loss in potential of about 35 % of the charging potential was then obtained. These experimental conditions are expected to meet the accuracy required for the purpose. Such stability checks have been made on 17 occasions, normalized to 0° C and 760 mm Hg. The mean of these checkings in volt per minute was 3.28 ± 0.9 %. The normalization factor was then maximum 1.147 and minimum 1.044.

Another important function needing investigation was the variation in response with the length of the irradiated portion of the unit. To investigate this function experimentally, the condenser dosemeter was provided with scale divisions, dividing the overall length (16 cm) into 8 equal parts, enabling the irradiated portion of the length to be 2, 4, 6, 8, 12, and 16 cm, all measured from the top of the capped ionization chamber. In these experiments 250 kV roentgen and $^{60}Co$ gamma radiation were used because these two types of radiation could be expected to produce evident effects. The results obtained are shown in Table 2.

It appears that the length of the irradiated portion slightly influences the response; to eliminate this effect it was therefore decided to use a standardized

**Table 1**

*Checking of the proportionality between response and radiation exposure from a radium gamma radiation standard source — Charging potential 400 V*

| Exposure time in min | Drop in potential | |
|---|---|---|
| | Percentage of charging potential | Volt/min at 0 C, 760 mm Hg |
| 15 | 11 5 | 3 3 |
| 25 | 19 0 | 3.29 |
| 35 | 26 8 | 3.31 |
| 45 | 31.2 | 3.29 |
| 60 | 45 5 | 3.28 |
| 81 5 | 61 7 | 3.29 |
| 90 | 67 9 | 3.28 |

Average 3 295 volt/min ± 0 6

obtaining equilibrium wall thickness when gamma radiation is to be measured The cap completely encloses the thimble and thus provides an effective mechanical protection This method of fitting the cap to the unit has been found both convenient and reliable The external diameter of the cap is the same as that of the condenser stem. The unit is otherwise of the same type as the one designed by the author in 1950 and since then used extensively and with good result at our institute

The air enclosed in the ionization chamber is always, by means of a small hole at the base of the thimble wall and cap wall in direct communication with the atmospheric air surrounding the unit We have for a long time used this method of avoiding differences between the pressure of the air in the cavity chamber and that of the surrounding atmospheric air as was mentioned in a paper as early as in 1941 (Thoraeus)

The stem of the unit is provided with a 6-sided brass ring to prevent the unit from rolling the ring is cut through at one place and must be slightly expanded when slid onto the stem It therefore works as a ring shaped spring and due to its light pressure against the stem surface and the resulting friction it will remain in position

One of the most important characteristics of the function of a condenser chamber dosemeter is the relationship between loss in potential and radiation exposure This loss in potential i e. the response should be proportional to the exposure This function was studied in the reference instrument by subjecting it to a test in which it was charged to 400 volt and then exposed to gamma

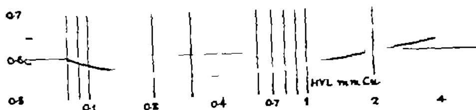



Fig. 3. Calibration factors of the reference instrument with capped chamber plotted against the half-value layers of conventional roentgen radiation.

stability (THORAEUS 1956). As long as the sealing is intact, the checkings are independent of the atmospheric conditions. The air in unsealed chambers must be in satisfactory communication with the surrounding atmospheric air. The instrument readings of the ionization in unsealed chambers produced by the incident beam must always be normalized to constant atmospheric conditions. This is achieved by multiplying the readings by a normalization factor usually called the NTP factor.

The readings of our own instruments are normalized to 0 C and 760 mm Hg. This normalization is preferred because it is the same as is used with the free-air standard chamber and thus means a uniform NTP procedure for all types of unsealed ionization chambers.

Exposures during our calibration procedure of condenser chamber units are usually adjusted to reduce the potential difference in each unit to about 60 of its initial value. The results of the calibration are given in terms of the calibration factor by which the instrument reading of the ionization in the chamber produced by the radiation exposure and normalized as mentioned

**Table 3**

*Calibration results of the reference instrument with capped chamber*

| Tube voltage kV | HVL of radiation mm Cu | Number of calibrations | Average of calibration factors R per div |
|---|---|---|---|
| 100 | 0.03 | 6 | 0.54 ± 2 % |
| 140 | 0.35 | 6 | 0.56 ± 1.2 |
| 175 | 0.9 | 6 | 0.57 ± 0.9 |
| 200 | 2 | 8 | 0.60 ± 1.1 |
| 250 | 3 | 6 | 0.61 ± 0.7 |
| $^{137}Cs\ \gamma$ | 10.7 | 5 | 0.67 ± 0.8 % |
| $^{60}Co\ \gamma$ | 14.8 | 9 | 0.68 ± 1.4 % |

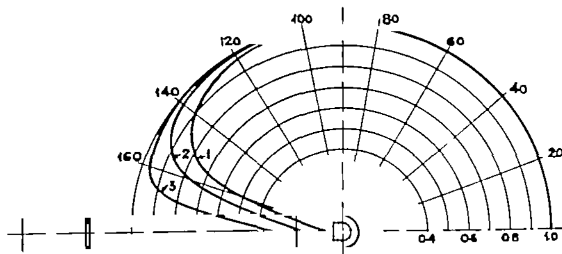



Fig 2 Direction dependence of the response to radiation of the reference instrument with capped chamber Air cavity indicated by dotted line.

Curve 1 100 kV roentgen radiation HVL = 0.09 mm Cu
Curve 2 250 kV roentgen radiation, HVL = 3 mm Cu
Curve 3 $^{60}$Co gamma radiation HVL = 14.8 mm Cu

field size of 10 cm × 10 cm. When the unit is positioned with the air volume at the field centre and the stem parallel to one of the sides of the field the length of the irradiated portion of the unit is 6 cm plus the width of the penumbra the latter may amount to 5 cm corresponding to an irradiated length of 11 cm The effect is then only about 1.5 % probably not more than 1 % due to the rapidly decreasing exposure rate in the outermost part of the penumbra region

The variation in response with the angle between the beam centre line and the longitudinal instrument axis the so-called direction dependence is not critical since the reference intrument is always used for exposure measurements free in air and with identical geometry (instrument perpendicular to the centre line of the beam) To obtain complete information on the properties of the instrument it was however found desirable to study also this function This was done by means of 3 types of radiation 100 kV and 250 kV roentgen and Co gamma radiation The results are given in the polar diagram of Fig 2 It appears that the direction dependence is small in the range between 0 to 120 degrees for all the three types of radiation in the range between 0 to 140 degrees for the 250 kV roentgen and the Co gamma radiation and in the range between 0 to 160 degrees for the $^{60}$Co gamma radiation

Ionization chambers may be of two different types hermetically sealed and unsealed It is advisable that both types be periodically checked to verify

following Using the geometry mentioned above the instrument with capped chamber was calibrated against the cavity standard for roentgen radiation of tube voltages between 100 and 250 kV constant potential, and for gamma radiation from $^{137}$Cs and $^{60}$Co The calibration results obtained on different occasions are collected in Table 3

The average calibration factors obtained by roentgen radiation are plotted against the half-value layers in the semilogarithmic diagram of Fig 3 which shows the so-called energy dependence of the chamber in that range of radiation energy

The function of the reference instrument was finally studied under conditions similar to those met with in clinical work. The instrument was charged to 399 volt and then irradiated during various times of exposure with a collimated $^{60}$Co gamma radiation beam, the cross-section of which was 10 cm × 10 cm and the exposure rate about 100 R/min, at 64 cm focal distance The loss in potential is plotted against exposure time in the diagram of Fig 4 The loss in potential is proportional to the exposure time up to about 370 volt and 2 65 mm, which corresponds to 139 7 volt/min. By means of the NTP factor 1 082, and the calibration factor for $^{60}$Co gamma radiation 0 66 R/volt (see Table 3) we obtain an exposure rate of 99 7 R/min. This shows that a 93 % discharge of the reference condenser chamber unit may be used under the above mentioned conditions without impairing the measurement result. When the above recommended discharge of only 40 % to 50 % is used, there is thus a rather wide margin. A 50 % discharge (200 volt) corresponds to a gamma radiation exposure of about 150 R.

The result of the test and calibration program provides a fairly complete survey of the most important properties of the reference instrument. The electrostatic leakage is small, usually a few tenths of a volt per hour and does not require any correction It is however checked by frequent observations.

The reference instrument and its properties were demonstrated at a Meeting of the Hospital Physicists from Denmark, Finland Norway and Sweden in March 1962. The normalization of clinical exposure measurements of high energy radiation in this group of countries was discussed by a separate Committee appointed by the Meeting The need for some kind of standardization was stressed by the representatives of the countries mentioned, and the possibility of having the reference instrument sent to all of them was considered The author offered the calibration facilities of the Institute of Radiophysics in Stockholm, including the loan of the reference instrument. The employment of the latter to establish the desired uniformity in clinical gamma radiation exposure measurements was considered the most convenient way then available, and was therefore recommended by the committee.

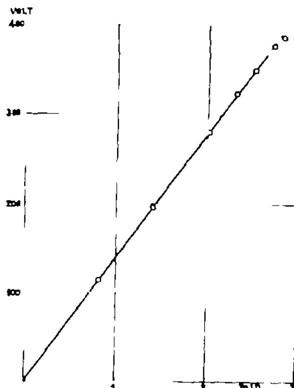



Fig. 4. Potential losses plotted against exposure time using collimated $^{60}Co$ gamma radiation beam at an exposure rate of 100 R/min.

must be multiplied to obtain the value in roentgen units for the radiation quality used.

Our calibrations with roentgen radiation are carried out by comparison with a cavity standard graphite chamber calibrated against four national free air standard chambers, one at our institute and three abroad (THORAEUS 1957). The comparison is based on equal readings of an integrating monitoring instrument, the stability of which in turn is checked by irradiation of its ionization chamber with gamma radiation from a radium source using standardized geometry.

The calibrations with gamma radiation are carried out in a collimated beam of the radiation in question (THORAEUS 1962) by comparison with the aforementioned cavity standard chamber and based on its calibration with $^{60}Co$ gamma radiation in 1956 at the NBS and with both $^{137}Cs$ and $^{60}Co$ gamma radiation by comparison with a transfer instrument (cf. ICRU Report 1959) lent to our standard laboratory by the NBS.

The calibration results of the reference instrument is presented in the

following Using the geometry mentioned above, the instrument with capped chamber was calibrated against the cavity standard for roentgen radiation of tube voltages between 100 and 250 kV constant potential, and for gamma radiation from $^{137}$Cs and $^{60}$Co The calibration results obtained on different occasions are collected in Table 3

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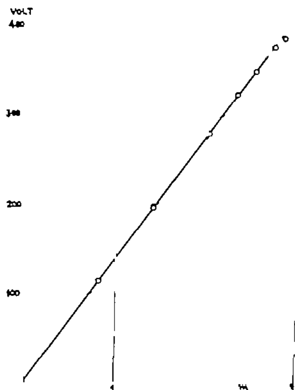



Fig 4 Potential losses plotted against exposure time, using a collimated $^{60}$Co gamma radiation beam at an exposure rate of 100 R/min.

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The calibration results of the reference instrument is presented in the

FROM THE DIVISIONS OF PHYSICAL CHEMISTRY AND NUCLEAR CHEMISTRY, ROYAL INSTITUTE OF TECHNOLOGY, THE DEPARTMENT OF ROENTGENOLOGY OF THE ROYAL SCHOOL OF DENTISTRY, STOCKHOLM, SWEDEN, AND THE HARVARD SCHOOL OF DENTAL MEDICINE, BOSTON, U.S.A.

# IODINE 125 AS A RADIATION SOURCE WITH SPECIAL EMPHASIS ON ITS APPLICATIONS IN MEDICAL RADIOLOGY

## I. Theoretical considerations

by

PER BERONIUS, SEVALD FORBERG, CARL O. HENRIKSSON and RUNE SÖREMARK

Radioactive nuclides have been used for many years as radiation sources in equipment for industrial purposes. Attempts have also been made to use roentgen and gamma radiations from various nuclides in medical roentgenography. Among the disadvantages of some of the radioactive nuclides, used for roentgen diagnostics in the medical field, have been the presence of gamma rays of undesirably high energy and hard beta radiation, in addition to the electromagnetic radiation of suitable energy. The high energy radiation requires heavy shielding and results in lower film contrast. The beta radiation requires a primary filter. Another disadvantage in medical roentgenography has been the difficulty of obtaining a radiation source of sufficiently small dimensions. Because of these and certain other disadvantages, the roentgen units constructed have not been widely used.

Submitted for publication 24 March 1964

## SUMMARY

An increasing number of dosemeters for radiotherapy in Sweden need calibration for gamma radiation. The most practical way to bring this about has been to construct a reliable condenser chamber dosemeter, easily transportable and sturdy enough to be sent to the radiotherapy clinics as a reference instrument. The instrument now available for this purpose is described.

## ZUSAMMENFASSUNG

Eine wachsende Anzahl von Tiefentherapie-Dosismessern in Schweden erfordern Eichung für $\gamma$-Strahlung. Dies könnte am zweckmässigsten dadurch ausgeführt werden, dass ein möglichst zuverlässiger Kondensatorkammer-Dosismesser hergestellt wurde. Ein solches Instrument soll leicht transportabel und genügend robust sein um zu den verschiedenen Therapikliniken als Vergleichsinstrument versandt werden können. Das Kondensatorkammer-Dosismesser wird beschrieben.

## RÉSUMÉ

Le nombre des dosimètres de radiothérapie qui, en Suède, doivent être étalonnés pour les radiations gamma, va croissant. Le moyen le plus pratique de réaliser cet étalonnage a été de construire un dosimètre chambre condensateur fidèle, facilement transportable et assez robuste pour être envoyé aux services de radiothérapie comme instrument de référence. L'auteur décrit le dosimètre construit dans ce dessein.

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the possibility of using Tm for the non-destructive inspection of light alloys and other materials within the thickness range of about 1 to 10 g/cm He also used radioactive americium, Am for producing a roentgenogram of a femur

Spangenberg & Pool (1953) published a roentgenogram obtained with Cs as the source, of the lower jaw of a dried skull. They concluded that the low intensities of roentgen rays did not permit clinical use of this material at that time and they continued It is a distinct probability however that further investigation will lead to the discovery of other radioactive X ray emitters which will produce an X ray beam of sufficient intensity and of proper wave length and one which will have a long enough half-life to make possible its clinical use as a source of X-ray radiations

Untermyer (1954) described a portable roentgen unit for Tm It weighed 3 1 kg and the dimensions were 4.5" × 2" (114 × 51 mm) In spite of the heavy shieldings, the dose rate at the surface of the unit was about 75 mr/hr Hasterlik (1954) by means of this unit produced roentgenograms of a hand, an ankle, and three teeth from a skeleton. Dennis & DeLuca (1954) used Tm (5 C) and Ce (15 C) for roentgenography of the hands and elbows of cadavers and living subjects. The source film distances were between 21 and 22 inches (53 and 56 cm) and the exposure times with no-screen film were 0.5 hours or longer Burke (1956) demonstrated a technique for the localization of renal calculi during surgical operations by means of a new Tm unit Stetoer & Westermark (1957) studied in some detail the radiation of Tm (Fig 1) and its absorption properties and discussed the possibilities of using the gamma and roentgen rays of Tm for industrial thickness measurements of various materials.

Spangenberg & Pool (1958) studied the possibilities of producing roentgenograms with Ce Eu, Sm La, Dy Dy Yb Gd, Pt, Au and W

Kellershohn (1963) investigated the applications of Hg

As a radiation source in roentgen diagnostics, I was introduced by Beronius et coll. (1962) and Myers (1962) and for forensic roentgenography by Henrikson et coll. (1962)

The use of beta emitters in combination with absorber material to produce roentgen radiation (Bremsstrahlung) suitable for medical and industrial roentgenography has been suggested by Lidén & Starfelt (1953) Kereiakes & Krebs (1954 and 1955) Kereiakes & Kraft (1956) and others.

Most investigators have used Tm in medical roentgenography About 76 % of the Tm nuclei disintegrate through 968 keV betas to the ground state of ytterbium 170 the smaller fraction, 24 disintegrates via 884 keV

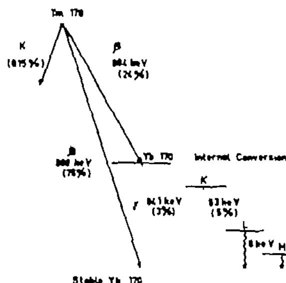



Fig. 1. The disintegration scheme of $^{170}$Tm (from STRIGER & WESTERMARK 1957)

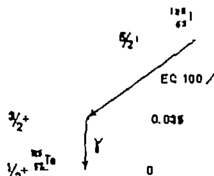



Fig. 2. The disintegration scheme of $^{125}$I (from KUNZ & SCHINTLMEISTER 1958)

The studies reported in this paper deal with the theoretical background of $^{125}$I as a roentgen source and represent continuation of earlier investigations on $^{125}$I (BERONIUS et coll. 1962 and HENRIKSON et coll. 1962).

The gamma radiations from some radioactive nuclides, e. g. $^{60}$Co, $^{192}$Ir, $^{137}$Cs and $^{170}$Tm, ranging in energy between 1.33 MeV (million electron volts) and 53 keV (kilo electron volts) have, as mentioned, been used as radiation sources for industrial radiography (BROWNELL 1961). However, of the nuclides used for industrial applications only those that seem to have influenced the field of medical roentgenography will now be mentioned.

SPANGENBERG (1948) produced a roentgenogram of three teeth by means of radiocesium, $^{137}$Cs. The radiation source was placed inside the oral cavity. No information was given concerning the size or activity of the source, nor of exposure times. MAYNEORD (1952) suggested the use of a radioactive source placed inside the body in order to obtain a clearer view of structures which become superimposed when conventional roentgenographic techniques are used. He discussed the possible application of radiothulium, $^{170}$Tm, in medicine and produced roentgenograms of a dried skull by means of this nuclide. The radiation source was about 3 mm in diameter. Though certain localized area of a living subject could be radiographed with an exposure time of only 5 minutes at a source film distance of 6 cm, the exposure times for other areas were often long, i. e. 10 to 11 hours at 12 cm. Screens, under the same conditions, reduced these exposure times to one hour. WEST (1953) demonstrated

the possibility of using $^{170}$Tm for the non-destructive inspection of light alloys and other materials within the thickness range of about 1 to 10 g/cm. He also used radioactive americium $^{241}$Am for producing a roentgenogram of a femur.

SPANGENBERG & POOL (1953) published a roentgenogram obtained with $^{137}$Cs as the source, of the lower jaw of a dried skull. They concluded that the low intensities of roentgen rays did not permit clinical use of this material at that time and they continued: It is a distinct probability however that further investigation will lead to the discovery of other radioactive X-ray emitters which will produce an X-ray beam of sufficient intensity and of proper wave length and one which will have a long enough half life to make possible its clinical use as a source of X ray radiations.

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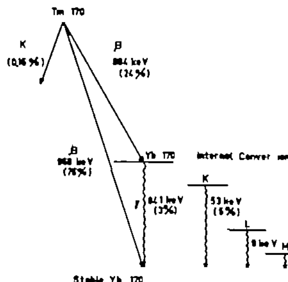



Fig 1 The disintegration scheme of ¹⁷⁰T (from STEHOLR & WESTERMARK 1957)

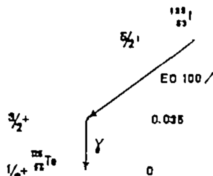



Fig 2 The disintegration scheme of ¹²⁵I (from KUNZ & SCHINTLMEISTER 1958)

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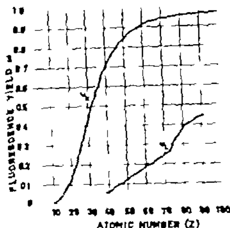



Fig 3. Fluorescence yield versus atomic number (from BLACK & WAY 1959

som authors, emits electromagnetic radiation having energies of approximately 33 54 80 and 134 keV The contrast of films obtained with radiation from Ce was considerably less than that obtained with radiation from a conventional dental roentgen machine (SPANGENBERG & POOL 1958)

## Physical properties of iodine 125

The decay scheme of I presented in Fig 2, has been taken from the nuclear data compilation of KUNZ & SCHINTLMEISTER (1958) The half life is 60.0 ± 0 5 days, and the nuclide decays to 100 by electron capture (EC) to excited Te followed by an isomeric transition (IT) of 35 keV to the stable ground level about 93 of this transition is however internally converted. The intensities and energies of the various radiations of I have been calculated nd are tabulated in Table 1

The energies of the roentgen rays were taken from FINE & HENDEE (1955) and the Auger electron energies have been calculated from the electron binding energies of tellurium as given in the nuclear data tables of STROMINGER et coll (1958) The intensities of the various radiations of I as calculated in Table 1 have been based on the conversion coefficients and EC ratios given in the two nuclear data compilations mentioned and on the fluorescence yield given by SLACK & WAY (1959) (see Fig 3 cf. MYERS & VANDERLEEDEN 1960)

As regards roentgen diagnostics, the most important radiation emitted

**Table 1**

*Calculated approximate disintegration table of ¹⁷⁰Tm*

| *Main processes* D t ut lized for th calculations | N mber of vacancies (i IT ) per 100 disintegrating nuclei K-shell | L-shell | Intensity (number of emissions per 100 disintegrating nuclei) | Energy (or energy l mits of resp. radiation group) k V | Type of radiation |
|---|---|---|---|---|---|
| *Electron capture (FC)* | | | | | |
| $EC_L/EC_K$ = 0.23 ± 0 03 neglecting $EC_M$ | 81 | 19 | | | |
| *Isomeric transition (IT)* | | | | | |
| Internal conversion (IC) | | | | | |
| K = 11 7 αK/ L = 7.3 | | | | | |
| assuming L/ M = 3 | | | | | |
| unconverted gammas | | | | | |
| 1/(Σ + 1) 100 | | | 7 | 35 | |
| $IC_K$ K/(Σ + 1) 100 | 79 | | 79 | 3 | IC |
| $IC_L$ | | 11 | 11 | 30 | eIC |
| $IC_M$ | | | 3 | 31 | eIC |
| L vacan les duced by K cancies | | 150 | | | |
| Total vacan ies i K a d L | 160 | 180 | | | |
| *Fluorescence* | | | | | |
| K fluorescen e t t l | | | 139 | | |
| K roentgen ray | | | 106 139 | 27 20 27 47 | XK |
| $K_\beta$ | | | 33 0 | 30 99 31 70 | XK |
| L » total | | | 24 | 3 76 1 37 | XL |
| Other roentgen rays | | | | 1 0 | X |
| *Auger electrons* | | | | | |
| From K vaca es | | | 22 | 21 9 31.8 | A |
| From L vacancies | | | 1 5 | 2 3 1 9 | A |
| From other vaca ies | | | | 1 0 | A |

betas to an excited state of ytterbium 170 The excitation energy 84 1 keV is partly dissipated as gamma radiation and partly by internal conversion IC The latter process results in the emission of characteristic roentgen radiation mainly with an energy of 53 keV but also with low intensity rays of 8 and 2 keV The two beta rays produce Bremsstrahlung from any material surrounding the thulium nuclei The disintegration scheme of ¹⁷⁰Tm as it was presented by STEIGER & WESTERMARK (1957) is shown in Fig 1

Another nuclide ¹⁴⁴Ce which has been suggested as a radiation source by

$A_Z$ atomic weight of element number $Z$
$\mu_Z$ linear absorption coefficient of element $Z$ in cm$^{-1}$ for the energy in question
$\varrho$ density of element number $Z$

The resulting linear absorption coefficient, $\mu$, of the source matter for radiation of the energy considered, can then be calculated as

$$\mu = \varrho \frac{\Sigma n_Z \mu_Z \varrho_Z^{-1} A_Z}{\Sigma n_Z A_Z} \tag{1}$$

where the summations are to be performed over all elements of the source. In the case where radioiodine has been deposited as AgI there is only one atom of silver ($Z = 47$) per atom of iodine ($Z = 53$), i.e. $n_{47} = 1$ and $n_{53} = 1$.

The atomic weights are $A_{47} = 107.9$ and $A_{53} = 126.9$, the densities are $\varrho = 5.67$, $\varrho_{47} = 10.5$, $\varrho_{53} = 4.93$ and the resulting linear absorption coefficient of silver iodide is

$$\mu = 5.67 \frac{\mu_{47} 10.5^{-1} 107.9 + \mu_{53} 4.93^{-1} 126.9}{107.9 + 126.9} = 0.248\mu_{47} + 0.62\mu_{53}$$

The intensity of the radiation in the direction of the axis of the cylinder can then be expressed as

$$I = \frac{\pi r^2 l \varrho \lambda N_A f \ln 2}{\Sigma(n_Z A_Z) 4\pi T_{1/2}} \eta_E Y_{c,a} \text{ quanta sec}^{-1} \text{ steradian}^{-1} \tag{2}$$

$Y_{c,a}$ is a factor for the average self-absorption correction which approaches unity for very thin sources (small $l$-values).

For a layer of infinitesimal thickness $dl$ at the depth $l$ the transmission to the surface in the perpendicular direction, or the differential yield, is

$$Y = e^{-\mu l} \tag{3a}$$

The transmission from the bottom layer

$$Y_{c,m} = e^{-\mu l} \tag{3b}$$

is defined as the marginal yield.

Integration from the surface to the depth $l$ over all differential yields gives the average yield for a source of length $l$

$$Y_{c,a} = \frac{1 - e^{-\mu l}}{\mu l} \tag{4}$$

Both the percentage marginal and average yields from a cylindrical source are plotted against the source length in units of $1/\mu$ and of $L_{1/2}$ (the half-absorption thickness) in Fig. 4.

### II. *Spherical radiation source*

For cylindrical sources with a large diameter as compared with the $1/\mu$ or $L_{1/2}$ value the intensity will be considerably lower in directions significantly deviating from the axial one. A source formed as a sphere therefore seems to have advantages for exposures over large solid angles. This form can for instance be obtained by sorption of radioactive ions in a particle of ion exchange resin.

during the decay of $^{125}I$ is the intense roentgen rays of about 27.4 keV. Due to low intensities and/or low energies, the unconverted gamma rays, the L, M and N roentgen rays, as well as the conversion and Auger electrons, are all of minor importance. These roentgen rays and electrons can easily be absorbed without any appreciable attenuation of the K roentgen rays. The gamma rays have an intensity of about 5 % of the intensity of the K roentgen rays, and an energy of only 8 keV more than the K roentgen energy. The presence of the gamma rays therefore produces no complications in most roentgenologic applications. In cases of high absorption, however, the transmitted gamma rays may be more intense than the roentgen rays because the higher energy is usually less attenuated.

## Strength of radioactive radiation sources

For many applications of radioactive sources, especially in medical radiology, there is a need for high intensity from a source of small dimensions in order to enable the combination of short exposure times and high resolution in the films. The intensity obtainable from a source of given cross section is however limited by the physical properties of the radiation and of the elements constituting the source. These principal limitations are generally not mentioned in current literature on radiation sources, wherefore a short presentation may be of value to readers who are not familiar with such calculations.

For purposes where isotropic intensity and a large solid angle are required, a spherically shaped source appears to offer the best choice, but when the only requirement is a narrow beam, a cylindrical source would seem to be just as satisfactory. As the latter design involves simpler mathematical formulas and constitutes an integral part in the calculations for a spherical source, it will be dealt with first.

### *I. Cylindrical radiation sources*

Let the radioactive nuclide be characterized by the following parameters:

$T$ half-life in sec

$\mu$ yield of radiation = number of emitted quanta per nuclear disintegration

$f$ specific activity expressed as the fraction of radioactive nuclides of the element in question

Further

$N_A$ Avogadro number ($6.02 \times 10^{23}$)

$\rho$ density of the source matter in g cm

$l$ length of the source cylinder in cm

radius (in the case of a circular cylinder) in cm

average number of atoms of element number $Z$ per atom of the active element in the source

where the first terms are

$$Y_{s,s} = 1 - \frac{3}{8}(2\mu r) + \frac{1}{10}(2\mu r)^2 - \dots \tag{8}$$

Thus $Y$ approaches unity for small values of the product $\mu r$ and this is so in the case of negligible self-absorption.

From eq (6) it is seen that at large values of $\mu r$ the yield $Y_{s,s}$ approaches the value $\frac{3}{4\mu r}$. This means that the intensity becomes proportional to the cross section of the sphere and corresponds to 100 % yield from a cylindrical layer of this cross section and $1/\mu$ cm thick. This might be expected for an infinitely thick source which expressed mathematically becomes

$$\lim_{\mu r\to\infty} I = \frac{\pi r^2}{4\pi\mu} \cdot \frac{e N_A f}{\Sigma n A_Z} \eta_r \frac{\ln 2}{T_{1/2}} \text{ quanta steradian}^{-1} \text{ sec}^{-1} \tag{9}$$

In the case of a cylindrical source the marginal yield was defined as the transmission from its bottom layer eq (3b) i. e. the ratio between the increments of the intrinsic and the external radiation intensities. This formulation can also be applied to a spherical source in which case the marginal yield is found to be

$$Y_{s,m} = \frac{1 - e^{-2\mu r}}{2\mu r} \tag{10}$$

The marginal and average yields from spherical sources are plotted against sphere radii in Fig. 4

## III Sources of $^{125}I$

Eqs (2) (4) (5) and (8) make it clear that in order to obtain the highest intensity from a small source the following four requirements should be fulfilled

1 The specific activity $f$ should be as high as possible, i. e the actual isotope should be available as carrier-free, and this is the case with $^{125}$I

2 The intrinsic yield of usable radiation $\eta_r$ should be as high as possible Being considerably more than 100 per cent, the roentgen ray yield from $^{125}$I is excellent.

3 The half-life should be short because it is inversely proportional to the activity/weight ratio in the case of carrier-free activities for practical reasons, on the other hand it should not be too short The 60 days half life of $^{125}$I seems to offer a well balanced compromise.

4 The source should be composed of as few and as light elements as possible, in addition to the radioactive one. According to this requirement, the elemental form would be the best choice although from safety considerations the choice is limited in practice to stable compounds of very low vapour pressure The compound should, in addition, enable a ready rendering as a small-sized source. In the case of $^{125}$I silver iodide and copper iodide seem to fulfill these requirements and will be investigated.

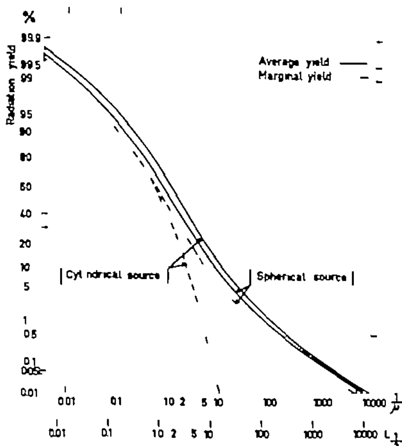



Fig 4 Average nd margi l yi lds in the lal d rection from cyli drical and spherical radiat on sources (on a normal distribution seal ) versus cylinder length d sphere rad i n u ts of $1/\mu$ ( n logarithm scale) An bscissa scale i also given in un t of $L$ the half value thickness. For a certai source ts length $l$ is d ded by th unit length $1/\mu$ for the particular radiation nd the curves re read for th correspondi g bscissa value e th merical alue of $\mu l$

Let $r$ denote the radius of the sphere in cm The radiation ntensit from this is then

$$I \quad \frac{4}{3}\,\frac{\pi r^{3}}{4\pi}\,\frac{\varrho\ \lambda_{A}\ f}{\ldots A_{c}}\ \pi\ \frac{\ln 2}{T_{\frac{1}{2}}}\ \eta_{s,a}\ \text{quanta steradian}\quad \text{sec} \tag{5}$$

Again $\eta_{s,a}$ is evaluated by integrat n over all volume elements of th sou ce and is fou nd to be

$$\eta_{s,a} \quad \frac{3}{2\mu}\left\{\frac{1}{2}\quad \frac{e^{-\mu r}}{2\mu r}\quad \frac{1}{(2\mu r)}\ \mu r\right\} \tag{6}$$

or after series exp nsi n of the exponential terms

$$\eta_{s,a} \quad 3\sum_{0}^{\infty}\left\{(-1)^{m}\frac{m+1}{(m+3)}\,(2\mu\ \ )\right\} \tag{7}$$

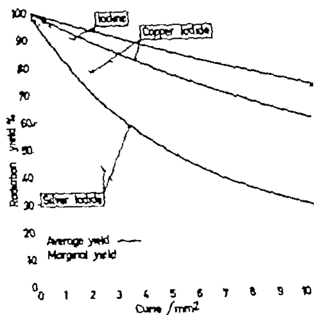



Fig. 5. Average and marginal radiation yields of 27.4 keV roentgen rays from elemental $^{125}I$, $^{125}AgI$ and $^{125}CuI$ sources versus source thicknesses in units of curies $mm^{-2}$. The yields are calculated for the axial direction.

As may be seen from Fig. 5, the *marginal yield* for a silver iodide source loaded with 2 curies per mm² *is 50 %*, a source of copper iodide must be three times stronger before *the* same self-absorption is attained.

*V. Fluxes from filter-equipped ¹²⁵I sources*

As may be seen from Tables 1 and 3 the *intensity of 3.8* keV roentgen rays is less than 5 % of the 27.4 keV *intensity* both for a copper and silver iodide source of 1 C/mm². In view of its contribution to the skin dose however this low-energy radiation is not so negligible as might be supposed from its low intensity. It is inferred from a slight extrapolation of a dose rate versus photon energy curve (SLACK & WAY 1959) that at the same quantum flux the dose rate from 3.8 keV roentgen may be 60 times higher than from 27.4 keV roentgen radiation. In order to reduce the relative skin dose contribution from the 3.8 keV radiation to a negligible level, *this* radiation must be further attenuated by a factor of about 30 *or more*. This filtering can be accomplished by for instance 0.03 mm of aluminium transmitting only 0.55 of the 3.8

**Table 2**

*Mass absorption coefficients ($\mu\varrho^{-1}$) of Ag, Cu, and I derived from Hodgman (1962) and Berry (1961) are tabulated for five different roentgen energies together with calculated mass absorption coefficients of AgI and CuI and linear absorption coefficients ($\mu$) of AgI CuI and $I_2$ (For comparison, the yields of other characteristic radiations from a source of 1 C $mm^{-2}$ are tabulated in Table 3)*

| | Primary radiation | | | Secondary radiation | |
|---|---|---|---|---|---|
| Energy in keV | 27.4 | 35 | 3.8 | 22.2 | 8.05 |
| Type of radiation | $K_\alpha$(Te) | $\gamma$($^{125}$I) | $L_\alpha$(Te) | $K_\alpha$(Ag) | $K_\alpha$(Cu) |
| $(\mu\varrho^{-1})_I$ $cm^2 g^{-1}$ | 12 | 33 | ~ 500 | 21 | 290 |
| $(\mu\varrho^{-1})_{Ag}$ | 53 | 26 | 1250 | 13.3 | |
| $(\mu\varrho^{-1})_{Cu}$ | 14 | 7 | 380 | | 51 |
| $(\mu\varrho^{-1})_{AgI}$ | 31 | 30 | 850 | 17.5 | |
| $(\mu\varrho^{-1})_{CuI}$ | 13 | 24 | 460 | | 210 |
| $\mu_I$ $cm^{-1}$ | 59 | 163 | ~ 2500 | | |
| $\mu_{AgI}$ | 173 | 170 | 4800 | 99 | |
| $\mu_{CuI}$ » | 73 | 135 | ~ 2600 | | 1 00 |

## IV Self-absorption of $^{125}$I sources

As may be seen from Fig 4 and eqs (3) (4) (6) and (10) the absorption coefficient must be known before the radiation yield can be calculated

Of primary interest in the present case is of course the yield of the tellurium K roentgen rays These have energy 27 4 keV and are so referred to below For certain purposes the yields of the 35 keV gamma rays and the 3 8 keV tellurium L rays may also be of interest Furthermore the copper and the silver in the iodide deposits and their backings will as secondaries, emit their own characteristic roentgen radiation upon absorption of the 27 4 and 35 keV radiations The attenuation of K roentgen rays of copper and silver 8 05 and 22 2 keV may therefore be of interest for the respective sources

The mass absorption coefficients of copper silver and iodine for the five energies mentioned were obtained by graphical interpolation of the values in Handbook of Chemistry and Physics (HODGMAN 1962) Some values for iodine were derived from the diagram of BERRY (1961) These coefficients are tabulated in Table 2 together with the resulting mass ($\mu\varrho$ ) and linear ($\mu$) absorption coefficients of elementary iodine copper iodide and silver iodide

One curie of the 60 days $^{125}$I in carrier free form weighs 57 3 $\mu$g and corresponds to 58 2 $\mu$g of natural iodine ( I) with respect to roentgen ray attenuation From this weight and the absorption coefficients of Table 2 the yields of 27 4 keV roentgen rays in the axial direction of cylindrical sources were calculated and plotted against source intensity in Fig 5

a resolution of 0 25 mm and better and this diameter was chosen for the present studies of the applications of $^{125}$I to dental roentgenography Whenever possible the source should be kept at a position that is three times the greatest film-object distance or more from the film in which case the corresponding resolving power will be 0 17 mm or better


## Acknowledgement

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## SUMMARY

Formulae are given for the intensities obtainable from both cylindrical and spherical sources constituted of any radioactive nuclide suitable for medical radiography The intense 27 4 keV roentgen rays emitted on the disintegration of $^{125}$I are discussed. The optimum source width is shown to be limited by the resolving power and exposure time requirements as well as by the cost of the radionuclide and the increased skin dose from proximal source

## ZUSAMMENFASSUNG

Es werden Formeln angegeben fur die Strahlungsintensitäten von zylindrischen und sphärischen radioaktiven Kernstrahlern, die fur die medizinische Strahlendiagnostik erwertbar sind. Die intensive 27 4 keV Strahlung, die beim Zerfall des $^{125}$I auftritt, wird besprochen. Die optimale Weite der Strahlenquelle ist einerseits durch das Auflösungsvermogen bestimmt und andererseits durch die Anforderung nach kurzen Belichtungszeiten Auch die Kosten des Kernstrahlers und die erhohte Hautbelastung bei kurzem Abstand verdienen Berucksichtigung

## RÉSUMÉ

Les auteurs indiquent des formules donnant l'intensité fournie par des sources cylindriques et sphériques constituées par l'un quelconque des corps radioactifs convenant à la radiographie médicale. Ils étudient l'intense rayonnement de 27 keV émis par la désintégration de $^{125}$I Ils montrent que le diamètre optimum de la source est limité par le pouvoir de résolution et le temps de pose ainsi que par le prix de ce radionuclide et par l augmentation de la dose cutanée quand la source est proche.


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The exposure time in medical roentgenography must be kept as low as possible. It is inversely proportional to the radiation intensity or, more directly expressed, inversely proportional to the dose rate at the film level.

In the case of radioactive sources like that of $^{125}$I the radiation intensity from a source of a given cross section is limited in practice by the self-absorption relations. The intensity obtainable under these conditions is proportional to the square of the source diameter; at the same time the dose rate at the film level is inversely proportional to the square of source-film distance. The dose rate at the film level is therefore proportional to the square of the relative source width, and the exposure time can, below a certain limit, be shortened only by increasing the relative width of the source. For the best choice between the contradictory demands on the relative source width, the resolution and exposure time requirements should be weighed against each other. It seems logical for most medical applications to satisfy the demand for resolving power at the expense of the exposure time.

The above may be summarized by stating that for sources of the same intensity per surface unit the resolution as well as the exposure time are constant for different source diameters, provided that the relative source widths are kept constant.

### III. *Relation between source cost and skin dose*

The cost of a $^{125}$I source, and of other radioactive sources too, may be expected to be nearly proportional to the total activity or to the square of the source diameter for a certain intensity per surface unit. From considerations of cost as well as for the sake of the total activity level, the smallest possible source diameter is desirable. Small sources require proportionally small source-film distances in order to maintain the minimum exposure time. There are, however, two main obstacles preventing the shortening of the source-film distance below a certain limit.

First, the geometry changes and the blur increases when the source-object distance is diminished.

Secondly, the local skin dose must be taken into consideration when using small source-object distances. Thus, when the distance between the source and the nearest part of the object is half the source-film distance, the dosage received by this part will be four times as large as for an infinite source-film distance. When the source-object skin distance is two-thirds of the source-film distance, the skin dose will be about twice that at an infinite distance. If the first condition, resulting in a four fold increase of the local skin dose, is accepted as the worse one, the resolving power will be half the source diameter or better. Under these circumstances a source diameter of 0.5 mm will yield

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# INHIBITION OF SKIN PENETRATION OF RADIOSTRONTIUM IN MICE BY AQUEOUS FATTY ACID GELS

by

KAI SETÄLÄ

The results of experiments in mice on th protective effect of an aqueous fatty-acid-salt gel against the skin penetration of radiostrontium are presented in this paper Investigations of this kind are well motivated as the integumentum commune is the part of the organism that is most open to exposure to radioactive isotopes, particularly those of strontium and iodine. In addition, everyday clinical experience and experimental data reveal that an almost countless number of substances of varying nature, electrolytes as well as non-electrolytes are absorbed by the organism through the intact skin.

The present report forms part of a wider research project started in 1945 and focused on the mechanism and factors involved in the percutaneous absorption in living animals, and skin penetration in animals specially killed, of environmental substances with different chemical and physical properties (see, for instance, ref. 18, 19 and 21—24)

Part of this work was supported by research grant from the State Medical Council of Finland. Submitted for publication 29 April 1964

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Fig. 1 Photographs from in vitro experiments. SOG was added to test-tubes containing aqueous solutions of $SrCl_2$. This resulted in changed colloid-chemical properties and led to the formation of a water-insoluble complex that looks like mycelium at the phase boundaries.

For autoradiography freshly prepared Ilford nuclear research emulsion K 5 was used. This emulsion is in gel form; its main grain diameter is 0.20 μ and it is sensitive to all charged particles.

The fatty-acid-salt gels used as protecting compounds (21, 22) were prepared by emulsifying pure, finely-divided sodium with or without potassium and with or without ammonium salts of certain fatty acids, preferably oleic, lauric, palmitic, and stearic acid. This was effected with distilled water aseptically and with mechanical techniques, at a temperature of approx. 45° C until the required homogeneity had been obtained. Emulsification was generally complete after 24 to 48 hours continuous shaking at 60 to 100 shakings/min, and about 300 hours additional self-stabilization. The process of emulsification was controlled by dark-field and fluorescence microscopy of samples taken from time to time during the shaking. The final product is a thermostable, gel-like colloid of the oil-in-water type: water is its external phase, i. e. the interfacial

*Material and Methods.* Descriptions have already appeared in the literature of the major features of the experimental techniques (18—26) on fluorescence microscopy (16, 18, 19, 24), autoradiographic aspects (3—5), on the terminology of the process of percutaneous transfer of substances (1), and some relevant aspects of colloid chemistry (11—13).

The experimental animals comprised about 250 adult male and female mice of the strains RA and Swiss CF No 1 with an average bodyweight of 27 g. The animals were given a standardized laboratory diet and water ad libitum. All mice used in the radiologic laboratory of this institute are kept in separate, isolated rooms and housed individually in special glass cages.

The investigation was carried out with reactor produced radiostrontium $^{85}Sr + ^{89}Sr$ (ref. 29) with the following physical data: $^{85}Sr$ half life 65 d, K, $\beta$, $\gamma$ 0.51 MeV, specific activity about 300 $\mu C/g$ Sr; $^{89}Sr$ half life 51 d, $\beta$ 1.46 MeV, $\gamma$ 0.91 MeV, specific activity about 190 $\mu C/g$ Sr. It was supplied as a solution in approx. 0.2N HCl. (A report now under preparation will present results obtained with carrier free strontium isotopes.)

Details of the methods used will be given in connection with the respective experiments. In taking specimens from the exposure area in the back, one half of each specimen was processed for histologic and autoradiographic examination. This involved a study both of frozen sections and of preparations embedded in paraffin. The other half of each specimen was used for quantitative determination of radioactivity in terms both of $\beta$- and $\gamma$-radiation (cf. motivations in references 6, 7, 26). The phase of the hair follicular cycle (anagen, catagen, telogen) was determined according to conventional criteria.

The samples were ashed in the usual manner for measurement of $\beta$ radiation in the skin specimens. The apparatus used in the activity determinations contained a $\beta$ end window-Geiger tube (type FHZ 15, Frieseke & Hoepfner GmbH, Erlangen, Germany); the counting unit was equipped with an automatic sample changer (types FH 49 and FH 449). When the activity of samples was low, a special low background, thin window, $\beta$-counting unit was used (types PW 4092, PW 4129/02, PW 18516 and PW 18518, Philips, Eindhoven, Holland).

Measurement of $\gamma$-radiation was done from native specimens without ashing. The apparatus contained a scintillator (type FH 421) with a thallium activated sodium iodide hole crystal (Quarz & Silice, Paris, France) of 2 in. outer diameter and 1 3/4 in. thick. The geometric factors were: 17 mm inner diameter, depth 38 mm. The shielding consisted of 400 kg of special lead and the background activity was continuously measured throughout the experimental period.



Fig 3 Mouse 1805. Fluorescence microphotograph of mouse skin 60 min after single post-mortem exposure of the back to MC. Unstained frozen section. The appearance differs essentially from that in fig 2, except for interfollicular epidermis and pilosebaceous apparatus, panniculus carnosus and other dermal organelles almost everywhere strongly fluorescent. Hair follicle cycle anagen. 150.

obtained in one such experiment are demonstrated in Figs 2 and 3 The test substance was an aromatic hydrocarbon (20-methylcholanthrene MC) dissolved in acetone the carrier power of which for aromatic hydrocarbons is particularly high (16 19 23) Skin biopsies were taken for study when the solution had been allowed to affect the skin for given lengths of time. Examination under the fluorescence microscope revealed that in the living animals (intra vitam experiments, Fig 2) the fluorescent material was chiefly encountered in the stratum corneum, perinuclearly in the cytoplasm of the cells in the interfollicular epidermis, and in the pilosebaceous apparatus. The corium and panniculus carnosus exhibited practically no specific fluorescence The situation was radically different in the dead animals (post-mortem experiments, Fig 3) The fluorescent material had penetrated through the epidermis and corium and spread all over the panniculus carnosus, whereas there was less in the pilosebaceous apparatus. Results obtained with 3 4-benzpyrene the fluorescence of which is about 4 times that of MC (see ref. 16, 19 23) were in complete accordance with the above.

It is therefore evident that when the mice were killed, essential modifications in or a total breakdown of, the capacity of the skin s absorption barrier occurred. The substances used — in this case fat-soluble aromatic hydrocarbons — could then easily traverse the epidermis and reach deep subepidermal organelles. The post mortem penetration was rapid These facts are advantageous the technique may be used for the study of penetration of



Fig 2 Mouse 1809 Fluorescence microphotograph of mouse skin 60 m n fter n gl ntra vitam exposure of the back to 20-methylchola thren (MC) l acetone. Unstained frozen section Locali ation of fluorescent material within stratum corneum interfollicul epidermis nd pilosebaceous pparatus. Hair follicula cycl nagen × 150

surface is concave toward the oil phase In the alkaline environment the colloid is of an association-colloid character (see general properties of these colloids e g in ref 11) The non polar group (light metal soap molecule) is oriented toward the oil phase whereas the polar group (carboxyl group and metallic radical) tends to be oriented toward the aqueous phase As soon as this colloid comes into contact with strontium isotopes, its colloid-chemical character is radically changed the emulsion is reversed into a water in-oil type oil is the external phase i e the molecules have turned so that the internal surfaces are convex toward the oil phase The surface tension of the solution grows and the strontium complex withdraws from the contaminated surface The formed strontium fatty acid complex (Fig 1) is water insoluble Conventional analyses showed that the complex contained all the strontium from the bulk solution

## Results

*Experimental study of percutaneous transfer of substances* The epidermis if intact has a negative electric charge, and the damaged skin a positive charge (8 9 15 27 30) As the chemical and physicochemical properties of a biologically active substance affect the rate of percutaneous absorption (cf ref 23) sug gestions have been made for the removal of the resistance at the cutaneous boundary to allow a free exchange of ions in all directions (cf ref 17)

Our own technique since 1948 (18) has also been based on attempts at elimi nating the effect of the percutaneous absorption barrier Hair from the back of mice was carefully clipped with scissors, without damaging the surface of the skin after which half of the animals were killed The substance was then administered to the skin area both of the living and the dead mice The results

Table 1

*Activity in skin samples expressed as β-radiation — pilot experiments*

| No. of series | No. of mouse | Treatment of skin with SOG in relation to exposure | Wet wt of skin sample (mg) | Activity in skin sample: Average total activity (pC) | Activity in skin sample: Activity ± SE (pC/mg ash) |
|---|---|---|---|---|---|
| *Aq. solution of 0.2 N HCl* | | | | | |
| | 30321 | None | 562 | 15,500 | 27.6 ± 1.6 |
| 1 | 30322 | None | 278 | 13,700 | 29.2 ± 2.6 |
| | 30323 | None | 382 | 14,100 | 37.1 ± 2.0 |
| | 30318 | Before and after | 580 | 1,950 | 3.4 ± 0.3 |
| 2 | 30319 | Before and after | 509 | 2,360 | 4.6 ± 0.3 |
| | 30320 | Before and after | 665 | 2,900 | 4.5 ± 0.3 |
| | 30306 | None | 465 | 32,000 | 68.6 ± 3.5 |
| 3 | 30307 | None | 277 | 19,000 | 68.5 ± 3.5 |
| | 30308 | None | 413 | 37,100 | 89.9 ± 4.6 |
| | 30309 | After | 399 | 5,970 | 15.0 ± 0.9 |
| 4 | 30310 | After | 414 | 7,120 | 17.2 ± 1.0 |
| | 30311 | After | 479 | 7,850 | 16.4 ± 1.0 |
| | 30312 | Before | 424 | 14,000 | 33.1 ± 1.9 |
| 5 | 30313 | Before | 518 | 11,900 | 22.9 ± 1.4 |
| | 30314 | Before | 610 | 17,000 | 27.9 ± 1.6 |
| | 30315 | Before and after | 393 | 3,930 | 9.1 ± 0.6 |
| 6 | 30316 | Before and after | 445 | 4,050 | 9.1 ± 0.6 |
| | 30317 | Before and after | 434 | 3,150 | 7.3 ± 0.5 |
| *Aq. solution of Tween 60* | | | | | |
| | 30342 | None | 345 | 15,100 | 43.7 ± 2.3 |
| 7 | 30343 | None | 791 | 23,600 | 29.8 ± 1.8 |
| | 30344 | None | 346 | 19,700 | 56.8 ± 2.9 |
| | 30348 | Before | 575 | 10,700 | 18.6 ± 1.0 |
| 8 | 30349 | Before | 628 | 9,110 | 14.5 ± 0.8 |
| | 30350 | Before | 602 | 6,870 | 11.4 ± 0.7 |
| | 30354 | Before and after | 599 | 3,820 | 6.4 ± 0.5 |
| 9 | 30355 | Before and after | 703 | 2,800 | 4.0 ± 0.3 |
| | 30356 | Before and after | 438 | 4,460 | 10.2 ± 0.6 |
| *Undiluted Tween 60* | | | | | |
| | 30345 | None | 306 | 5,920 | 19.4 ± 1.1 |
| 10 | 30346 | None | 348 | 7,930 | 22.8 ± 1.2 |
| | 30347 | None | 491 | 10,800 | 22.0 ± 1.2 |

radioactive isotopes into the skin Observation periods in post mortem experiments can be reduced and the effects of various sources of error (evaporation of the compound cutaneous excretion animal's licking) are consequently reduced On the other hand as the rate of cutaneous penetration is greater in dead than in living animals the testing of eventual protective procedures on the skin of dead animals adds an extra element of accuracy to the procedure

*Effect of protective compounds as determined on the basis of β radiation (pilot experiments)* These experiments had a dual purpose They were to show the significance for skin penetration of the carrier of the active material thus in the light of our earlier work on solvent effect (see for instance ref 16 19 23) and they were to provide us with controls Treatment generally consisted of a single local administration of Sr + $^{89}$Sr In experiments 1 and 2 the dose was approx 1 μC per mouse in experiments 3 to 17 5 μC, i e 5 times higher The carriers were an aqueous solution of 0 2 N HCl (experiments 1 to 6) a 25 % aqueous solution (experiments 7 to 9) undiluted Tween 60 (experiments 10 and 11) undiluted Span 20 (experiments 12 to 14) and reagent grade acetone (experiments 15 to 17) Tween 60 (polyoxyethylene sorbitan monostearate) and Span 20 (sorbitan monolaurate) are detergents i e surface active agents (Atlas Powder Co Wilmington Delaware USA) with hydrophile lipophile balance values of 14 9 and 8 6 respectively The animals were killed by ether-chloroform vapor after cutting of the hair and control of the intactness of the skin surface The cadavers, in series of three were fixed onto cork bases The active solutions were dropped with glass pipettes onto the back evenly spread with a glass rod and allowed to act for 15 min at an ambient temperature of 24 C The protective compound was a 1 per cent aqueous solution of sodium oleate in gel form (SOG) Skin biopsies were taken when the solutions had acted the excision line was beyond the exposed area and the skin was removed with a blunt instrument to avoid contamination The samples were then spread on blotting paper dermal surface down

The results as well as additional technical data have been collected in Table 1 The β activity in the control series of skin samples was highest in the series with 0 2N HCl and with acetone as carrier (experiments 1 3 and 15) Microscopic examination revealed that within the 15 min employed, the HCl solution had caused damage post mortem both to the stratum corneum and within the cell membranes in the epidermis proper Comparatively large quantities of the activity had thus been introduced into the skin Acetone again had carried Sr + $^{89}$Sr into the lipid framework of the cells and subcutaneous organelles Comparison of β-activity in the samples from experiments with a 25 per cent aqueous dilution of Tween 60 (experiment 7) and

film. Undiluted Span 20 is a thin oily solution and in spite of its lower hydrophile lipophile balance value Span 20 quickly penetrated the skin of the mice and carried with it the $^{85}$Sr + $^{89}$Sr it contained (experiments 12 to 14).

Table 1 indicates that skin treatment with SOG can, under the prevailing experimental circumstances, decrease the penetration rate of $^{85}$Sr + $^{89}$Sr to a highly significant ($P < 0.001$) degree as compared with a series without such treatment. Furthermore the protective effect was nearly independent of the mediator substance in which $^{85}$Sr + $^{89}$Sr was administered. Indeed experiments with radiostrontium in 0.2N HCl disclosed that treatment of the skin with SOG even after the administration of the active compound (experiment 4) rendered the $\beta$-activity highly significantly ($P < 0.001$) lower than in the corresponding control series (experiment 3). Activity in the skin was lowest when the back was treated with SOG both before and after exposure of the skin to $^{85}$Sr + $^{89}$Sr (experiment 6). When the radiostrontium was carried by a 25 aqueous dilution of Tween 60, the lowest $\beta$-activity in the skin samples was measured in experiments with the exposure area treated with SOG both before and after the administration of $^{85}$Sr + $^{89}$Sr (experiment 9). In experiments with Span 20 highly significantly ($P < 0.001$) lower activities were measured irrespective of whether SOG had been applied onto the skin before or after exposure to $^{85}$Sr + $^{89}$Sr (experiments 13 and 14). Even though acetone caused high penetration rates, the protective effect of SOG was evident. Highly significantly ($P < 0.001$) lower $\beta$-activities were thus measured both when SOG was applied onto the skin before the administration of $^{85}$Sr + $^{89}$Sr (experiment 16) and when it was applied after exposure (experiment 17). The SOG could thus reduce the penetration rate by a factor of 10 as compared with the corresponding untreated series (cf. experiments 17 and 15).

*It is therefore apparent that under the prevailing experimental conditions, even household detergents — to say nothing of acetone — caused a high rate of penetration of radiostrontium ($^{85}$Sr + $^{89}$Sr) into the mouse skin. The use of aqueous sodium oleate gel (SOG) as a protective compound, however highly significantly ($P < 0.001$) decreased the penetration rate into the skin as expressed in terms of $\beta$-radiation.*

*Effect of protective compound as determined on the basis of $\gamma$-radiation.* In this experiment the radiostrontium in an aqueous solution of 0.2N HCl was administered with a glass pipette onto the back of the killed mice as in the foregoing experiment. The protective compound was again SOG. The activity in the skin samples was measured on the basis of $\gamma$-radiation. The specimens were not ashed before determination of the radioactivity but native samples

Table I *(cont.)*

| No of series | No of mouse Carrier substances | Treatment of skin with SOC in relation to exposure | Wet wt of skin sample (mg) | Activity in skin sample | |
|---|---|---|---|---|---|
| | | | | Average total activity (pC) | Activity ± SE (pC/g ash) |
| 11 | 30351 | Before | 524 | 3 670 | 7.0 ± 0 4 |
| | 3033 | Before | 367 | 5 660 | 15 4 ± 0 3 |
| | 30333 | Before | 696 | 21 600 | 31 5 ± 1 7 |
| *Undiluted Span 20* | | | | | |
| 12 | 30324 | None | 377 | 11.500 | 30 4 ± 1 6 |
| | 30325 | None | 104 | 17 100 | 1.2 ± 2.2 |
| | 30326 | None | 128 | 9 310 | 21 7 ± 2.0 |
| 13 | 30330 | Before | 120 | 2.270 | 3 4 ± 0 4 |
| | 30331 | Before | 578 | 4 430 | 9.3 ± 0.6 |
| | 30332 | Before | 702 | 2 880 | 4 1 ± 0.3 |
| 14 | 30327 | After | 419 | 1.280 | 3 1 ± 0.3 |
| | 30328 | After | 187 | 1 990 | 4 1 ± 0.3 |
| | 30329 | After | 566 | 8.630 | 15.2 0.9 |
| *Acetone* | | | | | |
| 15 | 30333 | None | 612 | 30 900 | 50 5 ± 2 6 |
| | 30334 | None | 508 | 28.900 | 56.8 ± .9 |
| | 30335 | None | 319 | 18.500 | 53 1 ± 2.8 |
| 16 | 30339 | Before | 708 | 4 560 | 6.4 ± 0 4 |
| | 30340 | Before | 625 | 5,930 | 9.5 ± 0 6 |
| | 30341 | Before | 557 | 5.950 | 10.7 ± 0 6 |
| 17 | 30336 | After | 602 | 3 170 | 5.3 ± 0.3 |
| | 30337 | After | 580 | 3 000 | 5.2 ± 0.4 |
| | 30338 | After | 680 | 2 590 | 3 8 0 5 |
| *No exposure* | | | | | |
| 18 | 30360 | None | 625 | 34 | 0.1 |
| | 30361 | None | 638 | 14 | 0.1 |
| | 30362 | None | 709 | 15 | 0 1 |

with undiluted Tween 60 (experiment 10) as a mediator revealed that the penetration rate of the active material in the aqueous dilution was highly significantly ($P < 0.001$) higher than when the undiluted detergent was used This agrees with the results of our previous studies of the percutaneous transfer of surface active agents in general (cf ref 23) Undiluted Tween 60 is solid or semi-solid at room temperature and a considerable proportion of the agent and of the substance in it remained on the skin surface as a sticky



Fig. 4

Fig. 4 Autoradiogram of mouse skin (30308) 15 min after a single post-mortem exposure of the back. $^{85}$Sr + $^{89}$Sr in aqueous solution of 0.2 N HCl without SOG treatment. Chiefly transfollicular route of penetration and perifollicular accumulation of active material. Hair follicular cycle anagen. × 150.



Fig. 5

Fig. 5. Autoradiogram of mouse skin (30334) 15 min after a single post mortem exposure of the back. $^{85}$Sr + $^{89}$Sr in acetone without SOG treatment. In addition to transfollicular penetration, transepidermal entry of active material is also evident. Hair follicular cycle anagen. × 150

no attempts were made to prevent penetration of $^{85}$Sr + $^{89}$Sr into the skin the individual exposure areas had received 3.99 ± 0.30 pC per mg wet wt of skin tissue and per nC administered. In experiment 20 in which the skin was exposed for 15 min and then treated with SOG the average γ-activity amounted to 0.854 ± 0.070 pC. This means that the skin treatment with SOG resulted in a highly significantly ($P < 0.001$) lower activity than in the untreated controls (experiment 19) Finally in the series in which the skin was treated with SOG both before and after the 15 min exposure to $^{85}$Sr + $^{89}$Sr (experiment 21) γ-measurements disclosed that individual mice had been given considerably higher doses of activity than either of the two series above All the same the treatment of the skin with SOG had resulted in a highly significantly ($P < 0.001$) lower activity (1.45 ± 0.15 pC) than in the untreated controls (experiment 19)

It is therefore evident that analogously with the results of the experiments based on measurements of β-activity sodium oleate gel (SOG) highly significantly ($P < 0.001$) reduced the rate of penetration into the skin of radiostrontium ($^{85}$Sr + $^{89}$Sr) as determined on the basis of γ-radiation

**Table 2**

*Activity in skin samples as γ radiation — Carrier substance aqueous dilution of 0.2N HCl*

| No of series | No of mouse | Treatment of skin with SOG in relation to exposure | Wet wt of skin sample (mg) | Dosage per mouse (nC) | Activity in skin sample: Average total activity (nC) | Average activity (pC/mg wet wt/nC) | |
|---|---|---|---|---|---|---|---|
| | 32753 | None | 15.7 | 143 | 1[illegible].65 | 5.63 | |
| | 32754 | None | 19.1 | 113 | 11.15 | 5.09 | |
| | 32755 | None | 22.7 | 116 | 14.26 | 4.30 | |
| | 32756 | None | 16.0 | 157 | 11.18 | 4.45 | |
| | 32757 | None | 27.4 | 172 | 11.68 | 2.47 | |
| 19 | 32758 | None | 12.0 | 200 | 9.12 | 3.80 | 3.99 ± 0.30 |
| | 32759 | None | 19.4 | 199 | 14.61 | 3.78 | |
| | 32760 | None | 19.2 | 157 | 12.71 | 4.22 | |
| | 32761 | None | 23.1 | 141 | 10.14 | 3.05 | |
| | 32762 | None | 20.8 | 172 | 11.01 | 3.08 | |
| | 32763 | After | 21.8 | 153 | 3.22 | 0.965 | |
| | 32764 | After | 39.1 | 131 | 5.01 | 0.978 | |
| | 32765 | After | 31.6 | 168 | 5.44 | 1.025 | |
| | 32766 | After | 27.0 | 114 | 2.62 | 0.851 | |
| | 32767 | After | 28.1 | 144 | 4.10 | 1.013 | |
| 20 | 32768 | After | 27.1 | 132 | 2.60 | 0.727 | 0.854 ± 0.070 |
| | 32769 | After | 49.3 | 151 | 4.88 | 0.656 | |
| | 32770 | After | 40.6 | 158 | 4.43 | 0.691 | |
| | 32771 | After | 38.1 | 171 | 2.90 | 0.415 | |
| | 32772 | After | 22.8 | 139 | 3.76 | 1.186 | |
| | 32773 | Before and after | 25.2 | 169 | 7.96 | 1.87 | |
| | 32774 | Before and after | 31.5 | 153 | 7.62 | 1.58 | |
| | 32775 | Before and after | 34.6 | 154 | 7.38 | 1.39 | |
| | 32776 | Before and after | 28.7 | 137 | 2.83 | 0.72 | |
| | 32777 | Before and after | 45.6 | 151 | 9.21 | 1.34 | |
| 21 | 32778 | Before and after | 29.4 | 203 | 9.00 | 1.51 | 1.45 ± 0.15 |
| | 32779 | Before and after | 39.5 | 159 | 11.71 | 1.86 | |
| | 32780 | Before and after | 66.5 | 210 | 16.72 | 1.20 | |
| | 32781 | Before and after | 45.6 | 242 | 9.04 | 0.82 | |
| | 32782 | Before and after | 27.8 | 167 | 10.38 | 2.23 | |

were investigated as soon as they had been taken from the back of the mice The background activity in prolonged measurements was 110 imp/min

The experimental procedures and results are given in Table 2 In the control series (experiment 19) in which the skin was exposed for 15 min but

follicles were at rest, most of the active material entered the skin along the transepidermal route and a correspondingly lower quantity penetrated transfollicularly

Essentially different autoradiograms were obtained from the mice treated with SOG This accords perfectly with the results of the activity measurements. Fig 7 is an autoradiogram of a section of the skin treated with SOG (experiment 6, Table 1) A comparison of Figs 6 and 7 in which the hair follicular cycle is the same, discloses that the overall grain density in the SOG-treated skin (Fig 7) is clearly lower The grains appear to lie comparatively deep in the corium and their distribution is diffuse. This suggests, together with the fact that the hair follicles were at rest, that a major part of the active material had entered the skin transepidermally

It will be seen then that the autoradiographic results, which were in perfect accord with those obtained in the $\beta$- and $\gamma$-measurements, revealed that treatment of the mouse skin with sodium oleate gel (SOG) had distinctly reduced the rate of penetration of radiostrontium ( $^{85}$Sr + $^{89}$Sr) into the skin of the killed animals.

## Discussion

Considerations concerning the rate of percutaneous entry into the organism of substances from the environment must take into account a number of basic factors, above all the peculiar functions of the integumentum commune When percutaneous penetration is studied, the effect of the skin barrier on penetration has to be eliminated or reduced, for methodologic reasons (cf 18) This barrier system is located in the transitional zone between the cornified and the non-cornified epithelium the importance of a double electric layer in this zone has been emphasized (e. g 8—10 14 15 17 30)

The effect of the skin barrier was reduced in the present work by studying the entry of radiostrontium ($^{85}$Sr + $^{89}$Sr) into the skin of specially killed mice Two observations were made First, radiostrontium rapidly penetrated into the cutaneous structures in the form of $^{85}$Sr + $^{89}$Sr in different carrier substances (aqueous dilution of 0.2N HCl, detergents Tween 60 and Span 20 and acetone) Secondly treatment of the skin with aqueous sodium oleate gel (SOG) highly significantly ($P < 0.001$) decreased the quantity of $^{85}$Sr + $^{89}$Sr that entered the cutaneous structures. This was shown by measurements of radioactivity in skin samples in terms of both $\beta$- and $\gamma$-radiation, the results being in perfect accord. Autoradiography of the same specimens also yielded results directly comparable to those obtained by both techniques of activity



F g 6 Aut radiogram of ouse skin (30306) 15 fter single post m rten exposure of th back ⁸⁹S + ⁸⁹S in aqueous sol tion f 0.2N HCl without SOG treatment Both transepidermal and transfoll cula penetration accumulation of tive material even within corium and dermis. Hai follicula cycle telogen 150

Fig 7 Autoradiogram of mouse skin (30317) 15 min fter a single post mortem exposure of the back of the imal. ⁸⁹S + S n acetone. Pretreatment of th expos re area w th SOC The number of granules, ndicating th ctive material, is essentially lower than i utorad ograms bta ned after exposure without SOG treatment (cf figs 4 t 6) Hai f ll cular cycle telogen 150

*Effect of protective compound as determined by autoradiography* The skin penetration of radiostrontium was examined throughout the study by the radioautographic technique under standardized experimental conditions It appeared that an average exposure time of 60 days was most advantageous. Both frozen sections and sections from paraffin-embedded preparations were studied to obtain information about possible artificial phenomena during processing The sections were stained after the autoradiographic exposure The preparation of autoradiograms from mice treated with SOG and from the corresponding controls was carried out simultaneously and in the final light microscopic and autoradiographic assessments comparison was restricted to those skin samples in which the phase of the hair follicular cycle was the same

Figs 4 to 6 serve as typical examples of autoradiograms of skin exposed to Sr + ⁸⁹Sr but untreated with SOG the carrier substance was an aqueous solution of 0 2N HCl (experiment 3 Table 1) in Figs 4 and 5 and in Fig 6 it was acetone (experiment 16 Table 1) Analyses of the mode of percutaneous penetration of Sr + ⁸⁹Sr in the skin of the dead mice revealed that penetration is affected by the phase of the hair follicular cycle When the hair

and/or substances rendered soluble with them that the rate of percutaneous absorption is comparable to that of gastrointestinal absorption (see e. g. 17). The specific significance of the carrier substance — including those used for $^{85}Sr + ^{89}Sr$ in the present study — for skin penetration has also been directly demonstrated in this laboratory (e. g. 16, 23, 24).

5. The cutaneous surface is covered by a film composed of cholesterol and fatty acid esters and of waxes. These are good emulsifiers. Warm water in particular becomes easily miscible with this film and thus facilitates percutaneous penetration.

## SUMMARY

The percutaneous entry of radiostrontium and protective effect of an aqueous sodium oleate gel (SOG) against radiostrontium ($^{85}Sr + ^{89}Sr$) were studied in mice by quantitative measurements of $\beta$- and $\gamma$-radiation as well as by autoradiography. All the carrier substances used caused high penetration rate of $^{85}Sr + ^{89}Sr$ into the skin but its treatment with SOG decreased the degree of penetration highly significantly ($P < 0.001$). The results obtained by the measurements and autoradiography agreed.

## ZUSAMMENFASSUNG

Das perkutane Eindringen des Radiostrontiums und der Schutzeffekt eines wässerigen Gels von Natriumoleat (SOG) gegen radioaktives Strontium ($^{85}Sr + ^{89}Sr$) wurde an Mäusen sowohl durch quantitative Messung der $\beta$- und der $\gamma$-Strahlung als auch durch Autoradiographie bestimmt. Alle Trägersubstanzen verursachten eine starke Durchdringung der Haut des Strontiums ($^{85}Sr$ und $^{89}Sr$) aber Behandlung mit SOG verminderte (hoch-signifikant; $P < 0{,}001$) den Durchtritt. Die Messungen und die Autoradiographie zeigten übereinstimmende Resultate.

## RÉSUMÉ

L'auteur a étudié sur des souris, par les mesures quantitatives de rayonnements $\beta$ et $\gamma$ et par autoradiographie, la pénétration percutanée du radiostrontium ($^{85}Sr + ^{89}Sr$) et l'effet protecteur d'un gel aqueux d'oléate de sodium (SOG). Tous les excipients utilisés ont permis une importante pénétration percutanée de $^{85}Sr + ^{89}Sr$ à travers la peau, mais le traitement par SOG a diminué cette pénétration d'une façon très significative ($P < 0.001$). Les résultats des mesures de rayonnement et des autoradiographies ont concordé.

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measurement. The reliability of the present results is enhanced by the quantity of the material examined, the number of parallel determinations, the restriction of conclusions to instances of statistically highly significant ($P < 0.001$) differences, the use of a protective compound (SOG) with chemical and physicochemical properties desirable from a theoretical point of view, and the agreement of the observations with those of previous studies of percutaneous absorption and penetration in general. It must be emphasized that the results are actually even more conclusive because the experiments on the skin of dead mice favour the accumulation of greater than physiologic quantities of Sr + $^{90}Sr$ beyond the superficial barrier.

Comparison of the results with information in the literature gave them additional relevance and the salient features of the passage of substances may be briefly summarized as follows.

1. The skin is in itself capable of absorbing large amounts of various substances, such as alcohols, lipid solvents proper, salicylic acid, Hg, Pb, Sn, Bi and Sb salts, hormones, fat soluble vitamins, synthetic detergents, common soaps. Thus the rate of percutaneous entry, e.g. of Pb into the human organism, is of such an order that intoxication can occur. The percutaneous passage of $_1H$ (in the form of tritium oxide) applied to the skin in man occurs so fast that it can be detected in the urine in about 10 minutes (14). Experiments in animals have revealed that the quantity of $^{90}Sr$, $^{131}I$ entering the organism through the skin may be sufficient to kill the animal and its offsprings if it is pregnant (see e.g. 10, 12). Official pharmaca, especially certain Hg salts, yield further examples of agents whose application to the skin surface *leads to* a high-degree of penetration and a desired therapeutic effect on a remote target organ. As to the anatomical route of entry, transfollicular or transepidermal, experiments in newborn mice (0 to 10 hours of age) which lack pilosebaceous apparatus and whose epidermis is multilayered and thicker than in adult mice, as well as the employment of aromatic hydrocarbons as indicators of penetration, revealed that a substance applied to the skin immediately penetrates the epidermis (24), even if used in crystal form (16). It was further found in this laboratory (16) that the administration of urethan (a narcotic) to the intact skin of the mouse resulted in narcosis and ultimately in the death of the animal when certain detergents were used as solvents.

2. Numerous waste substances are excreted through the skin and are then capable of contaminating the outer skin surface from within.

3. The skin is capable of reabsorbing considerable quantities of *substances* from its own excretion.

4. Substances simultaneously soluble both in water and lipids (synthetic detergents, common soaps) penetrate the skin so rapidly, carrying adsorbed

and/or substances rendered soluble with them, that the rate of percutaneous absorption is comparable to that of gastrointestinal absorption (see e g 17) The specific significance of the carrier substance — including those used for $^{85}Sr + ^{89}Sr$ in the present study — for skin penetration has also been directly demonstrated in this laboratory (e g 16 23 24)

5 The cutaneous surface is covered by a film composed of cholesterol and fatty-acid esters and of waxes. These are good emulsifiers. Warm water in particular becomes easily miscible with this film and thus facilitates percutaneous penetration


## SUMMARY

The percutaneous entry of radiostrontium and protective effect of an aqueous sodium oleate gel (SOG) against radiostrontium ($^{85}Sr + ^{89}Sr$) were studied in mice by quantitative measurements of β- and γ-radiation as well as by autoradiography All the carrier substances used caused a high penetration rate of $^{85}Sr + ^{89}S$ into the skin but its treatment with SOG decreased the degree of penetration highly significantly ($P < 0.001$) The results obtained by the measurements and autoradiography agreed.

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## RÉSUMÉ

L auteur étudié sur des souris, par les mesures quantitatives de rayonnements β et γ et par autoradiographie, la pénétration percutanée du radiostrontium ($^{85}Sr + ^{89}Sr$) et l'effet protecteur d un gel aqueux d'oléate de sodium (SOG). Tous les excipients utilisés ont permis une importante pénétration percutanée de $^{85}Sr + ^{89}Sr$ à travers la peau, mais le traitement par SOG diminué cette pénétration d une façon très significative ($P < 0.001$) Les résultats des mesures de rayonnement et des autoradiographies ont concordé.


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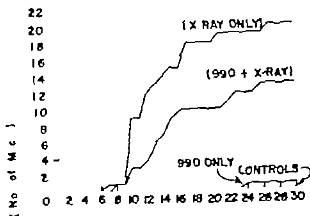



Fig 1 Experiment 1 compound "990" 400 mg/kg bodyweight.

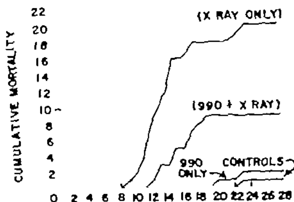



Fig 2. Experiment 2 compound "990" 400 mg/kg bodyweight.

of 0.5 mm of aluminum and giving a total single dose of 650 roentgen. This total dose is the LD 100 at 30 days for the strain of albino mice used

In experiments 1 and 2, the dosage of the drug was 400 mg per kg body weight in experiment 3, it was 200 mg per kg bodyweight. In each experiment an aqueous solution of drug was injected intraperitoneally 1 to 3 hours before irradiation

After injection of the drug the mice were marked according to a code system, so that they could be exposed in a random pattern and mice of all groups could then be mixed in the same cages for the period following irradiation This avoided any bias due to environmental influence The number of

FROM THE DEPARTMENTS OF DERMATOLOGY (DIRECTOR PROF J M KNOX) AND PATHOLOGY (ASSOC PROF R G FREEMAN) BAYLOR UNIVERSITY COLLEGE OF MEDICINE HOUSTON TEXAS U.S.A

# PROTECTION AGAINST IONIZING IRRADIATION BY CARBAMYL PYRAZOLE COMPOUNDS

by

JOHN M KNOX ROBERT G FREEMAN and DOUGLAS TROLL

Extensive studies of chemical protection against ionizing irradiation have revealed sulfhydryl compounds as the most effective among all the compounds tested e g benzophenones (KNOX et coll 1961) metabolic inhibitors, vitamins, *pyrimidines phenol derivatives, amines amidines and guanidines (THOMSON* 1961)

This paper reports the protective effect against ionizing irradiation of the experimental compound '990 (3 5-demethyl 1-dimethyl carbamyl pyrazole) (obtained from du Pont de Nemours Wilmington and designated du Pont compound 990 )

*Materials and Methods* Three experiments were performed to evaluate the protective effect of compound 990 against conventional roentgen radiation The irradiation source was a 200 kilovolt machine utilizing a half value layer

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## Results and Discussion

A protective effect by compound '990' is indicated by a survival rate of approximately 50 per cent. In experiments 1 and 2 using a dose of 400 mg/kg of compound '990' about one-half of the number of mice receiving both drug and roentgen irradiation survived, whereas virtually all those receiving only roentgen irradiation died by the 30th day (Figs 1 and 2) This confirmed the previous determination of the LD 100 at roentgen irradiation for 30 days in this strain of mice In experiment 1 only 13 of 21 drug treated and irradiated mice died. The results in experiment 2 were slightly better only 9 deaths in 21 mice No deaths occurred in the control group and only one mouse in the group receiving the drug alone died When a dose of 200 mg/kg bodyweight was given in experiment 3 only 14 of 21 mice died in the drug-treated and irradiated group, indicating some protective effect with half the original dosage (Fig 3)

It is interesting that a new class of chemical compounds can achieve a 50 per cent survival following a lethal dose of conventional roentgen irradiation. Continual testing of new compounds and modification of chemicals, known to be protective, offer hope of finding a truly effective protective agent against ionizing irradiation and justifies continual screening of new compounds.

The mechanism of action of these carbamyl pyrazole compounds is not known. The hypothermia produced by these agents is probably not sufficient to protect 50 per cent of the mice. However this may explain part of the protection since it is known that low temperatures reduce the effects of irradiation (Evans 1941 Carlson & Jackson 1959)

A related compound, 4-chloro-1-dimethyl carbamyl pyrazole (compound 1903') was tested similarily and gave only an insignificant amount of protection.

## SUMMARY

The protective effect of new experimental compound (3,5-demethyl-1-dimethyl carbamyl pyrazole) against ionizing irradiation has been demonstrated using the endpoint of LD 100 for 30 days with strain of albino mice. The protective effect of 200 mg/kg bodyweight was slightly less than that of 400 mg/kg which provided survival rate of 50 %. This new class of compounds shows promise and justifies further investigation to determine fully the protective effect of these and similar compounds.

## ZUSAMMENFASSUNG

Die Schutzwirkung einer neuen experimentellen chemischen Verbindung (3,5-Demethyl-1-Demethyl Carbamyl Pyrazole) gegen ionisierende Strahlung (LD 100, 30 Tage) wurde an Albinomäusen geprüft. Die Schutzwirkung war bei 200 mg/kg Körpergewicht etwas geringer als bei 400 mg/kg, wo die Überlebungsrate bei 50 % lag. Diese neue Gruppe von Verbindungen verspricht Erfolg und rechtfertigt weitere Untersuchungen, um die Schutzwirkung dieser und ähnlicher Verbindungen vollständig zu bestimmen.

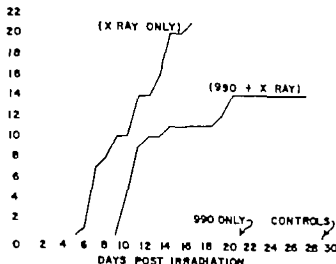



*Fig 3 E periment 3 compound 990 00 mg/kg body weight*

survivors and the number of deaths in each group were recorded daily for 30 days following irradiation

Four groups each containing 21 adult male mice were utilized in each experiment as follows

group 1 drug plus roentgen irradiation
group 2 roentgen irradiation alone
group 3 drug alone
group 4 control animals

*Pharmacologic data.* Compound '990 is liquid at room temperature Anal gesia and sedation may be produced in mice and rats given the drug orally or parenterally In rats the drug prevents dextran edema as well as burns caused by radiant heat and is strongly diuretic It can lower body temperature of rats in a dose related manner whereas it produces only a slight temperature change in dogs.

The compound is well tolerated by dogs rats, mice and guinea pigs when given orally or parenterally It is harmless to man in doses of 100 mg/kg body weight when given as 10 per cent saline solution intramuscularly or in oral doses of 200 or 400 mg/kg bodyweight An aqueous solution of the drug given intravenously has not harmed animals but has not been attempted in man The intramuscular dose of 400 mg/kg employed in these experiments is at the upper limits of tolerance and produces anesthesia

FROM THE DEPARTMENT OF RADIOTHERAPEUTICS (DIRECTOR PROF J S MITCHELL) AND THE SUB-DEPARTMENT OF VETERINARY ANATOMY (PROF J D BOYD) UNIVERSITY OF CAMBRIDGE, ENGLAND

# RADIOTHERAPY AND CHEMOTHERAPY FOR DOMESTIC ANIMALS

## III The treatment of non malignant conditions in dogs and cats

by

IAN A. SILVER and DONALD B. CATER

Chronic inflammatory lesions are common in animals, and are often very resistant to medical and surgical treatment. The resolution of indolent ulcers in man is sometimes hastened by small doses of roentgen rays and it seemed reasonable to explore their effects on similar lesions in domestic animals. An account of the response to γ rays of such lesions, in bone and soft tissues of the horse, has already been published (SILVER & CATER 1964 a). In the present paper the results of the irradiation of various chronic inflammatory lesions in dogs and cats, with roentgen and β rays, are reported. These lesions are especially common around the mouth, where they are subjected to constant irritation and trauma from licking. They are also frequent in the ears of dogs, owing to the rubbing of corrugations of the external auditory meatus against each other. Exostoses are usually found as a result of trauma but spinal arthritis with periarticular bony outgrowths often occur in long backed dogs. Keratitis

Submitted for publication 19 August 1963.

## RÉSUMÉ

L effet protecteur contre les radiations ionisantes d un nouveau dérivé expérimental (3,5-deméthyl 1-diméthyl carbamyl pyrazole) a été démontré sur une race de souris albinos en utilisant le point terminal de la DL 100 en 30 jours. L effet protecteur de 200 mg/kg de poids corporel a été un peu inférieur à celui de 400 mg/kg qui ont donné un taux de survie de 50 Cette nouvelle classe de composés est prometteuse et justifie d autres recherches pour déterminer exactement l effet protecteur de ces composés et des dérivés similaires.

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Chronic inflammatory lesions are common in animals, and are often very resistant to medical and surgical treatment. The resolution of indolent ulcers in man is sometimes hastened by small doses of roentgen rays and it seemed reasonable to explore their effects on similar lesions in domestic animals. An account of the response to γ rays of such lesions, in bone and soft tissues of the horse has already been published (SILVER & CATER 1964 a). In the present paper the results of the irradiation of various chronic inflammatory lesions in dogs and cats, with roentgen and β rays, are reported. These lesions are especially common around the mouth, where they are subjected to constant irritation and trauma from licking. They are also frequent in the ears of dogs, owing to the rubbing of corrugations of the external auditory meatus against each other. Exostoses are usually found as a result of trauma, but spinal arthritis with periarticular bony outgrowths often occur in long-backed dogs. Keratitis

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is a very common disease in dogs as their eyes are generally more exposed to such irritants as dust and grit than are human eyes The disease often becomes chronic and ulceration of the cornea is a frequent complication In many cases, where extensive vascularisation of the cornea has developed the lesions show considerable resistance to orthodox medical treatment.

*Technique* The problems involved in the application of roentgen therapy to animals have been discussed by SILVER & CATER (1964 b) Filtration was arranged to give maximum irradiation to the lesion

Beta ray therapy was carried out by using a flat 1 5 cm disc, $^{90}$Sr applicator on the end of an aluminium handle delivering 112 rad/sec. The animals were anaesthetised the eyelids held open with an eye speculum and the eye held in the desired position by tension sutures through the scleral conjunctiva During anaesthesia there was invariably a powerful ventromedial rotation of the eye ball which almost completely hid the cornea The third eyelid was retracted with forceps The surface of the cornea was lubricated with an aqueous local anaesthetic solution before the $^{90}$Sr was applied to the eye It was found convenient to insert the applicator under the eyelids but in some dogs the palpebral aperture was too small for this manoeuvre and then some skin reaction and epilation of the edges of the eyelids was seen it was never permanent however

Where the lesion was more than 2 mm thick it was removed completely or shaved down to a thin layer before the application of the $\beta$ rays This was particularly necessary in the case of some dermoids

The curvature of the eye even in a large dog is such that a flat applicator will only contact the cornea over a very short distance To obviate the danger of high dosage at one point and an inadequate dose on the periphery of the lesion the applicator was rocked with a circulator motion to ensure that it contacted the eye over its whole area Care was taken not to cause mechanical damage to the corneal epithelium by such movements

## Results

*Roentgen therapy* Typical responses of chronic inflammatory tissues in dogs and cats to treatment with roentgen rays are illustrated by the following case histories

*Case 1* Alsatian dog M 5 years, had a chronic granulating fibrotic ulcer (7 × 5 cm) on the side of nose and face with a 3-year-history of slow spread. Treatment 220 kV roentgen rays, 7 × 7 single field, 0 Cu/1 Al, MTD 250 r followed by nobecutane spray to minimise trauma from licking The ulcer shrank to one third of its original size in 6 to 8 weeks. Further treatment was refused and some ulceration persisted for 6 months.

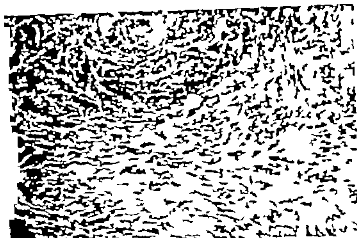


Fig. 1 Photomicrograph of chronic granulating ulcer of the nose of dog (Alsatian, Case 1) H & E. × 170.

*Case 2.* Cat, M. 5 years, had persistent ulcer (3 × 2 cm) on the upper lip and the nose, with 1 1 cm extension to the lower lip. It had failed to respond to repeated surgical and medical treatment over 2 years. Radiotherapy with 220 kV roentgen rays, 3.5 cm frontal field, 0 Cu/1 Al, MTD 250 r and 2.5 cm right lateral field, 1 Cu/1 Al, MTD 250 resulted in slow healing of the ulcer which was complete in 334 days.

*Case 3.* Cat, F. 7 years, with persistent ulcer 1 × 2.5 cm on the upper lip treated with 220 kV roentgen rays, 3.5 cm ○ frontal field, 1 Cu/1 Al, MTD 450. The ulcer healed in 60 days. Previous medical and surgical treatment over year had been unsuccessful.

*Case 4.* Labrador dog, M. 7 years, with an ulcer (3 × 2 cm) of the nose and nasal septum, persisting for more than year. Radiotherapy with 220 kV roentgen rays, 5 cm ○ 2 opposing fields, 1 Cu/1 Al, CTD 250 was followed by slow healing. A two thirds reduction of the area occurred in 52 days. Healing was complete in 78 days.

*Case 5.* Alsatian, M. 3 years, with chronic sinus discharge (3 × 4 cm) developed after removal of impacted left para-anal sacs. After failure of medical and surgical treatment, radiotherapy with 220 kV roentgen rays, 5 cm ○ frontal field, 0 Cu/1 Al, MTD 390 on day 0 and 910 on day 119 was followed by some improvement. The animal developed second sinus on the right side and was subsequently destroyed as it became savage. The treated sinus never healed completely.

*Case 6.* Alsatian, M. 7 years, with similar lesion (4 × 4 cm) and history as in Case 5. It was treated with 220 kV roentgen rays, 5 cm ○ 0 Cu/1 Al, MTD 320 on day 0 and 800 on day 130, which resulted in a very slow filling of the cavity with healthy granulation tissue. Healing was obvious after each treatment but complete resolution did not occur till day 317




Fig 2 Roentgenograms of k ll of dog (Case 9) ) At th ge of 9 months, a d b) at the ge of years (15 months fter treat ent w th 755 of 220 kV roentgen ray )

*Case 7* Spaniel dog M 11 years, with a chron fibrotic granuloma (6 × 6 × 2 cm) of hard palate vith extensions to upper lip and nose It had recurred twice after surgery bled constantly and interfered with respiration Treatment was given w th 220 kV roentgen rays, 15 × 10 cm, 1 Cu/1 Al in 3 fields frontal 990 r right lateral 335 r and left lateral 335 r gi ng CTD 1 660 r The mass shrank slowly and the general condition of the dog improved At day 250 tl e animal was destroyed because of age and general infirmity The lesion wa still present but inact ve and l ea ily fibrosed

*Case 8* Alsatian M ? years post traumat c exostoses of radiocarpal ntercarpal and carpomet carpal joints, over 5 5 cm w th some limitat on of carpal flexion to half of normal movement, 16 months after a road accident. Treatment with 220 kV roentgen rays to a 7 7 cn f ontal field 0 Cu/1 Al, MTD 240 r resulted n improved carpal flexion after 170 days and full movement after 330 days.

*Case 9* West Highland dog 1 9 months with bilateral exostoses of the petrou temporal bones and posterior borders of mandible associated w th excessive salivation and d fficult in swallowing Rad otherapy with 220 kV roentgen rays, 5 cm 0 Cu/1 Al, two l teral fields giving MTD 755 r to eacl petrou s bone was followed by no further extension of bony outgrowths and improved jaw movement Excess salivation persisted

The commonest lesions treated were ulcers around the mouth. In 4 of 5 cases there was a diminution in size of the ulcer following radiotherapy with doses of 250 r and in 3 of these 4 there was complete resolution The fifth case (Case 7) was a chronic granuloma with extensive fibrosis. This was treated with a much larger dose (CTD 1 660 r) which had a beneficial effect. The lesion became smaller and inactive but never healed

Cases 5 and 6 with ulceration of the anal sacs, represent a common condition in dogs. These ulcers are constantly contaminated by faeces and are irritated by rubbing from the tail They are often very resistent to orthodox treatment. Radiotherapy appeared to accelerate healing of these ulcers but the response was not very spectacular

The effect of roentgen rays on two non-malignant bony conditions in dogs is illustrated by Cases 8 and 9 The former showed a periosteal reaction after trauma which limited carpal movement. A small dose of 220 kV roentgen rays (320 r) with 1 mm Al filtration was followed by cessation of further growth of exostoses, remodelling of the new bone already present, and restoration of carpal movements. Case 9 is of a completely different kind. The bilateral outgrowths of the petrous part of the temporal bone appear to have some genetic basis. The condition was known to have occurred previously in the family of this particular dog — it had been lethal because movement of the lower jaw eventually became impossible. The small dose of radiation (755 r with 1 mm Al filtration) was tried as an experiment and was followed by cessation of the growth of the bone. However the animal was near the age when natural growth of the skull would be expected to cease anyway

*Beta ray therapy* This has been applied to a variety of eye conditions in dogs, especially those involving extensive vascularisation of the cornea and dermoid cysts. The number of cases treated, the doses given and the results obtained with the various lesions, are given in a Table.

Superficial vascularisation (pannus) was often so extensive as to render an animal completely blind and in the majority of cases was present in both eyes. These cases usually responded well to treatment, which was carried out in 3 or 4 fractions at intervals of 2 to 3 weeks. It was noted that if longer intervals were used, the response was less satisfactory — but it was not possible to use shorter intervals on more than a few (5 cases) as most of the animals came from considerable distances. In the few cases treated with 3 fractions at 4-day intervals the response was not obviously better The first signs of regression of blood vessels was seen 2 to 4 weeks after the initial treatment and complete clearing of the cornea usually took from 6 to 8 weeks. It was noticed in several cases (9 out of 24) that although the keratitis resolved the accompanying con-

Table

*Response of eye lesions to radiotherapy*

| Lesion | Number of cases | Dosage in rad | Response to treatment | | | Recurrence within year |
|---|---|---|---|---|---|---|
| | | | Complete remission | Some improvement | Nil | |
| Pannus | 27 | 9 000—1 000 | 23 | 1 | 3 | 8 |
| Interstitial keratitis | 19 | 4 × 3 000 | 8 | 4 | 7 | 3 |
| Dermoid cysts | 6 | 2 × 3 000 | 5 | — | 1 | — |
| Keratitis pigmentosa | 6 | 3 × 3 000 | 0 | 4 | 2 | 3 |

junctivitis did not In 8 of these 9 cases there was a recurrence of the keratitis at intervals ranging from 4 to 18 months after the first treatment Four cases out of these 8 have shown repeated recurrence of superficial vascularisation which regressed after each treatment but reappeared again in 8 to 12 months. Pigmentation in the areas previously covered by pannus has been seen in 12 out of 24 cases which responded to treatment These 12 include all 8 of those in which there were recurrences It is not clear if this pigmentation is deposited merely in the course of the resolution of chronic inflammation or if it is accentuated by the radiation

The response of interstitial keratitis is not so satisfactory and deep blood vessels do not appear to be so affected by beta rays as blood vessels in the corneal conjunctiva Very frequently the smaller vessels regress but the larger ones do not. However as there is some improvement in more than 50 % of cases, it seems reasonable to try $\beta$ ray therapy on this condition

*Dermoid cysts* The animals in which these occurred were all young Direct irradiation of the cysts was followed by cessation of growth but there was little or no regression except in one case The best results were obtained by irradiation of the tumour site following surgical removal of the majority of the growth. The dermoids which are listed in the table had all recurred after surgery

*Keratitis pigmentosa* This condition gave a poor response to beta ray therapy It had been present for 1 to 2 years in all cases treated and in no case was there complete remission. Four of six cases showed some response but this was confined to a reduction of the vascularity and there was no indication of removal

of pigment. Conversely there was no obvious increase in pigment. Most of the cases which showed improvement relapsed within one year of the first treatment with $\beta$-rays.

## Discussion

Radiation therapy for non-malignant conditions in animals seems justified when orthodox medical and surgical treatment has failed. The risk of inducing leukaemia by radiation therapy can be taken with greater equanimity in the case of an animal as opposed to human subjects.

The useful clinical effects of small doses of roentgen rays, such as are reported here, are difficult to explain. In the case of indolent ulcers the radiation seems positively to stimulate epithelialisation, and it presumably slightly alters the delicate balance between granulation tissue and skin, in favour of the latter In horses, where exuberant granulation is a much greater problem than in the dog, much larger doses of radium $\gamma$-rays have had to be used to discourage connective tissue proliferation in chronic wounds.

The case of the puppy with exostoses of the petrous bones is interesting because of the familial history of the condition. It is open to question whether the radiation was responsible for arresting the growth of the bone or whether the exostoses stopped growing naturally at the same time as skull growth was completed. It is hoped to be able to repeat the treatment on a younger animal from this family to see if a low dose of radiation during the period of active skull growth will arrest the development of the exostoses. The case of post-traumatic exostosis (Case 8) responded in much the same way as similar lesions which we have treated in horses.

Another common condition of dogs, chronic otitis externa with ulceration and proliferation is also alleviated by radiotherapy but as it is easily treated by surgery which usually results in a permanent cure, it is hardly justifiable to use roentgen rays unless surgery is definitely contra-indicated

The application of $\beta$-ray therapy to lesions of the eye has been reported by FRIEDELL, THOMAS & KROHMER (1951) LEDERMAN (1952, 1956 1957) SEALE 1953) MERRIAM (1956) TROTT & WHEATLEY (1956) and FRASER & NAUNTON (1961) in man, and by CANDLIN & LEVINE (1952) CATCOTT & GRIESNER (1954) and DALTON (1958) in the dog and by CATCOTT THARP & JOHNSON (1953) and WHEAT BLACK, HAGE & RHODE (1954) in cattle and horses. Our results are broadly similar to those already reported but we found that at least 3 weeks elapsed before any response was discernible in cases of keratitis, which is in contrast to the 3 to 7 days mentioned by DALTON (1958) for the same conditions. CANDLIN & LEVINE (1952) used very large doses (20 000 rad) in

a single application but in the few cases in which we gave 10 000 rad at once there was considerable radiation reaction 10 to 12 days later

The danger of producing permanent damage to the eye by radiation largely concerns cataract formation Cataract is common in old dogs and especially in those with diabetes The range in tissue of $\beta$ radiation from $^{90}$Sr is too short for more than a small percentage of the dose to reach the lens. With $\gamma$ radiation or 220 kV roentgen rays the safe dose has yet to be determined In man CHARTERIS (1940) reports that damage to the lens is a rarity after a dose of 1 500 r and a certainty after 2 800 r ALDEN JONES & RANKIN (1949) used doses of up to 1 000 r for corneal ulcers without trouble, and SEALE (1953) treated 16 cases of carcinoma of the corneal limbus in man with 2 500 to 3 525 r radium $\gamma$ rays and calculated the dose to the lens which varied between 800 and 1 380 r in the different cases They state that no damage occurred to the normal adult lens However COGAN & DREISLER (1953) reported that one out of three patients given 600 r 200 kV roentgen rays will develop cataract and MERRIAM & FOCHT (1957) found that the minimum cataractogenic dose was 200 r SILVER & CATER (1964 b) irradiated both eyes of a dog with 940 r 220 kV roentgen rays and a year later repeated the treatment with 960 r No cataract formation has been observed

With regard to $\beta$ radiation of the eye FRASER & NAUNTON (1961) report good results after 1 000 to 2 000 rep in human cases where the vascularisation of the cornea is superficial as in acne rosacae keratitis but much less effect when the vascularisation was of the deeper vessels which is in agreement with our findings With regard to the late effects of beta radiation on the eye MERRIAM (1956) reported radiation cataract after 2 300 to 22 000 rep tel angiectasis after 3 000 to 5 000 rep superficial keratinisation of the conjunctival epithelium (5 000 to 10 000 rep) superficial punctate keratitis (5 000 rep) iritis, iris atrophy vascularisation and scarring of the cornea after much larger doses (20 000 to 30 000 rep)

## Acknowledgements

Our thanks are due to Col J Hickman, Dr L W Hall and Mr M C G Littlewort of Cambridge University School of Veterinary Medicine for referring some of the cases to us, and to Professor J S Mitchell for his continued help and encouragement One of us (D B.C.) received full time support from the British Empire Cancer Campaign for Research.

## SUMMARY

Chronic non-malignant proliferative conditions in 7 dogs and 2 cats were treated with 220 kV roentgen rays. Beta radiation (6 000 or 12 000 rad) was used to treat eye conditions in 58 dogs (pannus 27 cases, interstitial keratitis 19 dermoid cysts 6 and keratitis pigmentosa 6)

## ZUSAMMENFASSUNG

Chronische, nicht-maligne, proliferative Erkrankungen wurden an 7 Hunden und 2 Katzen mit 220 kV Röntgenstrahlen behandelt. Beta Strahlen kamen zur Anwendung um bei 58 Hunden Augenerkrankungen zu behandeln (27 Fälle mit Pannus, 19 mit interstitielle Keratitis, 6 dermatoide Zysten, 6 Fälle mit Keratitis pigmentosa).

## RÉSUMÉ

Sept chiens et deux chats atteints d'affections chroniques proliférantes bénignes ont été traités par roentgenthérapie sous 220 kV. Des affections oculaires (pannus 27 cas, kératite interstitielle 19, kystes dermoïdes 6, et kératite pigmentaire 6) ont été traitées chez 58 chiens par les radiations bêta.

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# ATTENUATION OF GAMMA RADIATION FROM $^{60}$Co, $^{137}$Cs, $^{192}$Ir AND $^{226}$Ra IN VARIOUS MATERIALS USED IN RADIOTHERAPY

by

R. Thoraeus

The attenuation of gamma radiation in different materials is of general interest in many kinds of radiotherapy and clinical radiophysics work. The materials used may be broadly divided into three groups (1) water and tissue-equivalent materials, (2) conveniently available metals with properties that make them suitable for HVL measurements, and (3) heavy metals suitable for wedges, for compensating and flattening filters, and for radiation protection.

Group (1) is of main importance in clinical radiophysics work, such as in experimental studies of the dose distribution obtained by different irradiation techniques, and for the production of isodose diagrams. The human body has then to be substituted by special 'phantom bodies' either made of a homogeneous, tissue-equivalent material, or produced by moulding such a material on a skeleton to achieve an anatomically correct imitation of the human body.

The materials in group (2) must be non-corrosive and commercially avail

From the Institute of Radiophysics (Director Prof. R. Sievert) King Gustav V Jubilee Clinic Karolinska Sjukhuset, Stockholm, Sweden Presented at the Meeting of the Nordic Society of Medical Radiology at Helsingfors, Finland, in June 1964 Submitted for publication 25 June 1964

able in a pure state, at low or very moderate cost and in convenient dimensions. The materials most commonly used are aluminium and copper lead although in general too soft for the purpose is nevertheless sometimes employed

Heavy metals such as lead tungsten and uranium are mainly used for source heads and local screening of the radiation in desired directions. They are, however too expensive for protective barriers, such as walls and flooring in which instances concrete and the still better iron-ore concrete are mostly used Lead can to some extent be used in special cases when additional protection is required for example in doors The attenuation of gamma radiation from radium $^{60}$Co and $^{137}$Cs in iron-ore concrete was discussed in a previous paper (THORAEUS 1960) to which the reader is referred for further information Stainless steel though not a very heavy material, is frequently used for various parts of equipment and was therefore included in the study

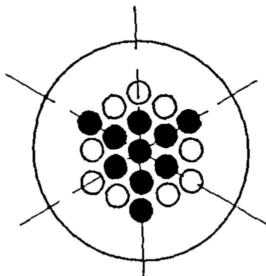
Tungsten has a density of about 19 3 and a melting point of about 3 370 degrees centigrade. It is technically produced by pressing the metallic powder *into rods. These are at first fired then sintered at a temperature close to the* melting point and finally mechanically treated by hot swaging in a high speed hammer machine Such pure tungsten is so hard that it cannot be machined by edge tools. Within certain limits, however it can be brought into desired shapes by high temperature hammering or cold grinding This tungsten material is not used for radiotherapeutic purposes except as anode material in certain accelerator tubes for the production of roentgen radiation

There is however another material called tungsten heavy alloy which is produced from tungsten powder with a small percentage of a metallic adhesive usually copper and nickel This material has a density of up to about 18 and can be machined by all types of tempered steel edge tools. As the price per unit weight is 50 to 60 times higher than that of lead the employment of this material is mainly confined to source heads and applicators in which the required screening effect has to be obtained with small dimensions The tungsten heavy alloy was included in the present investigation

To be reasonably defined the attenuation has to be referred to a collimated *narrow beam geometry the experimental arrangements are* therefore briefly described in the following

The attenuation measurements of the gamma radiation from $^{137}$Cs and $^{60}$Co were made by the sources and collimating equipment described in a recent paper (THORAEUS 1962) The collimator used gives a beam cross-section of about 10 cm in diameter at a focal distance of 100 cm The $^{137}$Cs source is about 10 mm in diameter and the $^{60}$Co source about 6 mm

The $^{192}$Ir source was an activated iridium wire 5 mm in length 0 5 mm in diameter and encapsulated in aluminium of 1 3 mm thickness. The attenua



Radium cassette, with radium containers (black spheres) arranged symmetrically as hexagon. The circles indicate spare holes to enable an increase of the number of radium containers to maximum of 19 within the same source diameter of 34 mm.

tion measurements were carried out about 80 days after the activation, the half-life being 74 4 days.

The Ir gamma radiation spectrum is complex and wide It comprises at least 17 lines of energies from 136 to 1 066 keV some of these contribute however very little to the total emission. The three lines 296, 308 and 317 keV are responsible for 61 6 %, the line 468 keV for 23 1 and the three lines 588 605 and 613 keV for 10 6 % i. e. in all 95.3 , of the emission. An effective energy of 380 keV may be calculated from all the spectral lines and their percentage contribution.

A special conical lead collimator about 170 mm long has been constructed for the radium source. It has a small recess at its base, in which an aluminium cassette containing 10 short radium containers is positioned. These containers are of the type that has been introduced and described by SIEVERT (1932) and were previously used in so-called teleradium units each contains about 50 mCi, and the radium substance enclosure is double-walled, consisting of 0.35 mm Au + 0.3 mm Pt, and equivalent to 0 62 mm Pt. The external dimensions are 5 4 mm (diameter) and 10 mm (length)

The cassette consists of a disc-shaped central body of aluminium, 53 mm in

able in a pure state at low or very moderate cost and in convenient dimensions. The materials most commonly used are aluminium and copper lead although *in general too soft for the purpose is nevertheless sometimes employed*

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down to at least 20 %. The resulting percentage attenuation values were at first plotted against the corresponding thicknesses in a diagram, and the first and second half value layers were then obtained by interpolation.

The results obtained are collected in the Table, which shows the first and second half-value layers in millimeters. For comparison the table also includes the first half value layers of water and pure metals calculated from the NBS Circular 583 (GRODSTEIN 1957)

The attenuation of monoenergetic radiation in water enables the calculation of half value layers and their plotting against the radiation energy in a diagram. By interpolation of the experimental half-value layers of the iridium and radium gamma radiations in the diagram, we get 380 kV and 1 15 MV respectively

The ratios between the half value layers for $^{137}$Cs and $^{60}$Co gamma radiations are given in the last column of the Table. It appears that this ratio is 0 72 to 0 76 for materials of low atomic numbers but only 0.51 to 0.58 for materials of high atomic numbers. This verifies that shielding and collimation by high atomic number elements is relatively more effective for the $^{137}$Cs gamma radiation than for the $^{60}$Co radiation.

It is further of interest to note that the first half value layer obtained with radium gamma radiation is somewhat smaller than that of the cobalt radiation. This shows that the radium radiation components of lower energy than cobalt predominate at such a moderate attenuation. With attenuation factors corresponding to the second half value layer and factors of importance in radiation protection techniques, the radium radiation components of higher energy than that of cobalt become predominant the material thickness required to give the same attenuation factor thus becomes greater than that of the cobalt radiation (THORAEUS 1960) It is found, from the attenuation curve of the radium gamma radiation in copper however that a first half value layer equal to that of the $^{60}$Co gamma radiation (14 8 mm Cu) can be obtained by adding a filter of 6.5 mm copper but the exposure rate is then reduced by about 30 per cent.

Plexiglas and presdwood are frequently used as materials for homogeneous phantoms. It appears, however from the table that the attenuation power of these materials is different from that of water

The soft tissue equivalent material used by Alderson Research Laboratories to produce average man equivalent phantoms was included for comparison. This material is said to consist of a thermosetting iso-cyanate rubber physically and chemically adjusted to an effective atomic number of 7.30 and a density of 0.985 but the attenuation power is different from that of water In fact, polystyrene and mix D show the greatest water-equivalent attenuation power of the materials investigated.

**Table**

*Half-value layers in millimeters of various materials for 4 different gamma radiation sources*

| Material | Density | $^{60}$Co First HVL | $^{60}$Co Second HVL | $^{60}$Co HVL NBS | $^{137}$Cs First HVL | $^{137}$Cs Second HVL | $^{137}$Cs HVL NBS | $^{192}$Ir* First HVL | $^{192}$Ir* Second HVL | $^{226}$Ra First HVL | $^{226}$Ra Second HVL | HVL-Cs / HVL-Co |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Water | 1.00 | 108 | 109 | 108 | 82 | 82 | 81 | 63 | 68 | 106 | 119 | 0.75 |
| Mix D | 0.98 | 112 | 113 | — | 80 | 80 | — | 63 | 69 | 109 | 120 | 0.72 |
| Alderson material | 0.99 | 117 | 118 | — | 89 | 88 | — | — | — | 111 | 123 | 0.76 |
| Pressdwood | 1.03 | 121 | 121 | — | — | — | — | — | — | — | — | — |
| Polystyrene | 1.05 | 107 | 107 | — | 80 | 81 | — | 63 | 67 | 105 | 117 | 0.75 |
| Plexiglas | 1.18 | 96.5 | 96 | — | 71 | 70 | — | 56 | 58 | 93 | 100 | 0.73 |
| Aluminium | 2.70 | 46.5 | 46.5 | 46.7 | 34.5 | 34.5 | 34.0 | 27 | 28.5 | 43.4 | 49.4 | 0.73 |
| Stainless steel | 7.89 | 16.5 | 16.4 | — | 11.9 | 11.8 | — | 8.8 | 9.2 | 15.4 | 16.5 | 0.72 |
| Copper | 8.90 | 14.8 | 14.8 | 14.9 | 10.7 | 10.7 | 10.7 | 7.6 | 8.0 | 13.6 | 15.5 | 0.72 |
| Lead | 11.25 | 10.5 | 10.6 | 10.5 | 5.5 | 5.6 | 5.68 | 2.2 | 2.8 | 8.0 | 11.0 | 0.54 |
| Tungsten alloy | 17.74 | 6.85 | 6.92 | — | 4.0 | 4.1 | — | 1.7 | 2.4 | 5.5 | 7.1 | 0.58 |
| Uranium | 18.76 | 5.63 | 5.67 | 5.66 | 2.85 | 2.90 | 2.89 | — | — | 4.2 | 5.9 | 0.51 |

Encapsulated in 0.35 Au + 0.50 Pt equivalent to 0.62 mm Pt

* Encapsulated in 1.5 mm Al

diameter and 10 mm thick in which holes have been drilled to receive the radium containers. Each side of the body is covered by a 1 mm thick disc of the same material and diameter and kept in position by three screws. The external thickness of the cassette is thus 12 mm.

The cassette body is schematically shown in the figure. The radium containers are arranged in hexagonal symmetry forming a source of maximum 34 mm in diameter. The number of radium containers may be increased to 19, corresponding to about 950 mCi without increasing the diameter.

The radium collimator is inserted into a cylindrical lead block of adequate protection value. Its collimating opening is closed by an easily removable, full length lead plug.

Preliminary studies of the attenuation of gamma radiation from the $^{137}$Cs and $^{60}$Co sources were reported in previous papers (THORAEUS 1961, 1962). The studies have later been repeated and considerably extended and now comprise attenuation of gamma radiation from the four above mentioned radioisotopes in 12 different materials.

Each beam of gamma radiation was attenuated by the different materials

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# EARLY HEMATOLOGIC EFFECTS OF WHOLE-BODY 14 MEV NEUTRON IRRADIATION IN MICE

by

M. L. DAVIS, E. B. DARDEN JR. and G. E. COSGROVE

Effects of radiation on the peripheral blood of mammals have been reported for neutrons (HENSHAW et coll. 1946, 1947; JACOBSON 1947; JACOBSON et coll. 1947, 1949; EVANS 1948; SOKOLOV 1958), gamma rays (HENSHAW et coll. 1946, 1947; JACOBSON et coll. 1947, 1949; SMITH et coll. 1962) and roentgen rays (JACOBSON 1947; JACOBSON et coll. 1947, 1949; BRECHER et coll. 1948; ROSENTHAL 1955; HULSE 1961; ROGH and PARDO 1963), but such information on the effects of 14 MeV neutrons is fragmentary (STORER et coll. 1957). While studying the late effects of 14 MeV neutrons in mice we also investigated the blood picture in such animals as compared with those exposed to roentgen rays. The results from this blood study are reported here.

*Materials and Method.* Female RF/Up mice, 10 to 11 weeks of age, were divided into 5 experimental groups and exposed to 0, 50, 100, 200, or 400 rad

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## SUMMARY

The attenuation of gamma radiation from $^{137}Cs$, $^{60}Co$, $^{226}Ra$, and $^{192}Ir$ has been studied experimentally using narrow beam geometry in 12 different materials of interest in radiotherapy and in clinical radiophysics work. The results given are the first and second half-value layers.

## ZUSAMMENFASSUNG

Der Schwächungsquotient der γ-Strahlung von $^{137}Cs$, $^{60}Co$, $^{226}Ra$ und $^{192}Ir$ wurde experimentell für 12 Stoffe die von radiotherapeutischem oder medizinisch-physikalischem Interesse und am engen Strahlenbundel ermittelt. Die Resultate werden für die erste und zweite Halbwertschicht angegeben.

## RÉSUMÉ

L'atténuation des rayonnements gamma de $^{137}Cs$, $^{60}Co$, $^{226}Ra$ et $^{192}Ir$ a été étudiée expérimentalement avec un faisceau étroit sur 12 matériaux différents qui présentent un intérêt en radiothérapie et en radiophysique clinique. Les résultats publiés sont les premières et dernières couches de demi-absorption.


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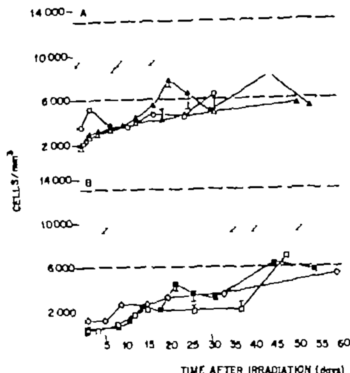



Fig. 2. Lymphocyte counts in RF female mice receiving roentgen or 14 MeV neutron radiation. Symbols as in fig. 1. The vertical bars indicate 1 standard error of the mean for selected points.

Beginning on the 1st day after irradiation, and at intervals thereafter hematologic studies were made on 3 to 10 mice from each group. All blood samples were obtained by clipping the end of the tail and were taken between 10 a. m. and 1 p. m. The studies included determination of packed red cell volume (microhematocrit) total leukocyte count and differential white blood cell count. Doubly oxalated 32 × 0.8 mm capillary tubes were used for packed red cell volume determinations. Three hematocrit tubes were obtained for each mouse sealed with Critoseal (from Aloe Scientific, St. Louis, Missouri, U.S.A.) and centrifuged for 6 minutes at 12 000 rpm. The measurement of packed cell volume was made on a micro-capillary reader. A differential leukocyte count from each mouse was made on the basis of 100 cells in a selected area of the slide. All blood smears were stained by the Wright-Giemsa technic. Standard chamber methods were used for determining total leukocyte number

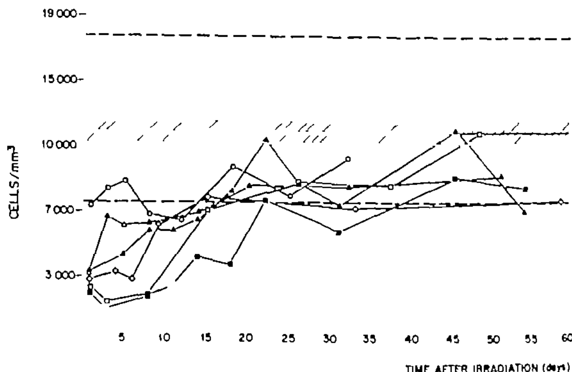



Fig 1 Total leukocyte ount in RF female mice exposed t roentgen rays or 14 MeV neutrons. Each point represents 5 to 10 mice.
— — — — control range //// mean control value with range of 2 standard errors of the mea ○ 50 rad △ 100 rad ▽ 200 rad, and □ 400 rad 14 MeV eutrons ▲ 100 rad, and ■ 400 rad 300 kV roentgen rays.

14 MeV neutrons. The radiation was produced by the deuterium tritium reaction in a Cockcroft Walton accelerator Conditions of dosimetry have been described (CONGER et coll 1958) During exposure each mouse was held in an individual cylindrical nylon container with 1/16 walls, containing small ventilating holes. These containers were mounted at a distance of 20 cm from the target on a circular brass frame During exposure the assembly was rotated slowly (3 rpm) around the target so that each mouse received radiation to all sides at a dose rate of approximately 1 to 1 5 rad/min Control mice received similar rotation in the assembly Several months later 3 other groups were exposed to 0 100 or 400 rad roentgen rays The physical factors were 300 kV 20 mA, *inherent filtration 0 1 mm Al with 2 mm Al added filtration* 0 385 mm Cu HVL, 93 to 94 cm target to-mouse distance dose rate approximately 90 r/min The exposure cage was rotated in the radiation field at 8 rpm The controls were rotated in the exposure cage but the roentgen beam was not turned on After irradiation the animals were housed in lots of 10 per cage and allowed free access to Purina laboratory chow and drinking water

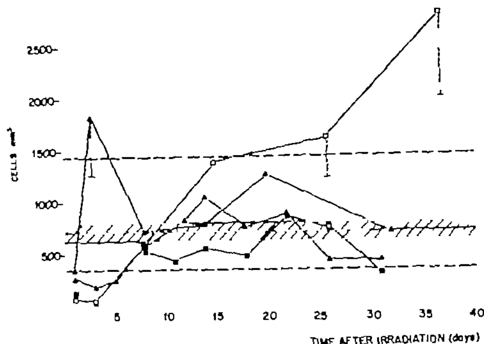



Fig. 4 Monocyte counts in RF female mice receiving roentgen or 14 MeV neutron radiation. Symbols as in fig 1

(Fig 2, A and B) Lymphocytes did not attain control levels in any group except the 100 rad roentgen group during the first 30 days. At the end of this period, there was still moderate to marked reduction in the mean counts of the other groups tending to vary in relation to the radiation dose. During the 2nd month, however there was a gradual upward trend in mean lymphocyte counts towards normal. In all groups receiving doses of *100* rad or more, occasional lymphocyte abnormalities were noted, consisting of cell enlargement, cytoplasmic basophilia, or rarely nuclear bilobation.

*Neutrophils* On day 1 there was a considerable depression in the neutrophil count in all groups except the 50 rad neutron group. Thereafter neutrophil counts in the 50 and 100 rad neutron groups did not deviate from normal during the period of study Neutrophil counts in the other groups remained depressed until between the 6 to 12th day (Fig 3) The counts then rose and in the 400 rad neutron group overshot the control level. The percentage of band neutrophils in the blood of control mice was 4 to 8 % In irradiated groups receiving 400 rad of neutrons or roentgen rays, this percentage rose as high as between

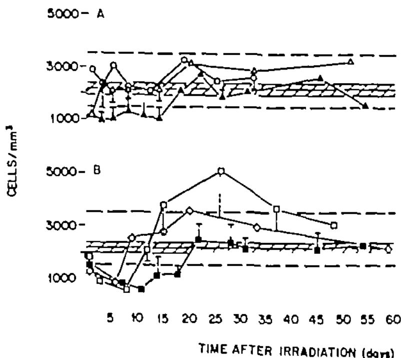



Fig. 3. Neutrophil counts in RF female mice receiving roentgen or 14 MeV neutron radiation. Symbols as in fig. 1.

The hematologic data for each animal were recorded on data cards and this information was then transferred and stored on IBM cards from which the analyses were made by machine.

## Results

*Mortality.* No 30-day mortality was noted except after 400 rad of neutrons, which killed about 10 % of the exposed mice.

*Total leukocytes.* The counts on the 1st day indicated a marked fall in total leukocytes which increased with dose in both neutron and roentgen irradiated groups (Fig. 1). By day 3 there was some return toward normal at the lower dose levels (50, 100 rad neutron and 100 rad roentgen) but the counts remained low at the higher dose levels until between days 6 and 11. The lowest mean count noted was 960 cells/mm³ and was observed in the 400 rad roentgen irradiated group at 3 days. Counts tended to rise progressively after the 11th day, even at the higher dose levels, and were within lower normal limits by the 22nd day in all the groups.

*Lymphocytes.* The postirradiation curves followed the general outline of the curves for total leukocytes in both neutron and roentgen irradiated groups

## Discussion

Total leukocyte, granulocyte, lymphocyte, and monocyte counts were initially depressed in relation to radiation dose in all groups. Recovery of all depressed cell lines seemed to be in progress from days 6 to 8 to about day 20 at which time neutrophil and monocyte counts approximated normal. Lymphocyte counts, however, did not return fully to normal at the high dose levels until the 2nd month after irradiation. Injury of erythropoietic tissue was manifested by a slight fall in packed red cell volume during the 2nd week at the higher doses, and by increased polychromatophilia with all doses. These hematologic changes are characteristic for acute whole-body irradiation (JACOBSON 1954).

Quantitative differences in hematologic effects between 14 MeV neutrons and roentgen rays were inconsistent. The depression of the lymphocyte count following neutrons appeared to be more prolonged than that following roentgen irradiation (Fig. 2), but the granulocytopenia was of longer duration (Fig. 3) and the anemia more marked (Fig. 5) after roentgen irradiation. On the basis of these data, therefore, the RBE varied with the parameter under consideration. The marginal statistical significance of these differences, however, would not allow us to conclude that the RBE of the neutrons was really different from that of roentgen rays. The differences observed are, nevertheless, consistent with earlier observations on the RBE of 14 MeV neutrons for acute effects on hemopoietic tissues, which indicated values of 1.5 to 1.7 for splenic and thymic atrophy in mice, and a value of 0.84 for depression of iron 59 uptake by red blood cells in rats (STORER et coll. 1957). From these results, we may tentatively postulate that the tendency towards slower recovery of lymphocyte counts in our neutron-exposed mice, as compared with those exposed to roentgen rays, may have been correlated with greater injury of the thymus, spleen, lymphoid, and other soft tissues by neutrons, whereas the faster recovery of neutrophil counts and less marked depression of hematocrit in the same animals may have been correlated with less severe injury of their bone marrow. The effect of the considerable difference in dose rate of the two forms of radiation on their parameters is not known. That neutrons of lower energy would have shown a higher RBE for injury of the marrow seems probable from the studies of DAVIS & COLE (1961).

## SUMMARY

Mice were exposed to 50 to 400 rad of 14 MeV neutrons or 100 to 400 rad of roentgen rays. Determinations of total and differential leukocytes and hematocrit values were made. A correlation of leukopenia to roentgen dose was observed and reached maximum within

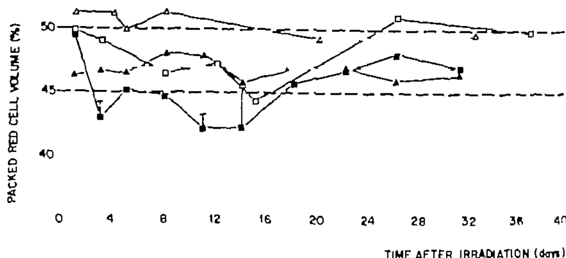



Fig. 5. Packed red cell volume in RF female mice receiving roentgen or 14 MeV neutron radiation. Symbols as in fig. 1

18 and 26 % on days 8 to 26 after irradiation. Morphologic changes in neutrophils consisted of a shift to the left, basophilic inclusions, basophilia of cytoplasm and some cell enlargement.

*Monocytes.* The 100—400 rad groups showed depression of monocyte counts on day 1 in relation to dose (Fig. 4). The counts rose to normal levels within the next several days and from the 6th day on all groups were within or above normal limits. In the early days after exposure there was an increase in cytoplasmic inclusions in monocytes in all irradiated groups.

*Packed red cell volume.* The 400 rad roentgen group showed depression of packed red cell volume during the 2nd week on days 11 and 14 dropping to a value of 42, about 12 % below control values. There was a tendency for depression also in the 400 rad neutron group, the level being reached on day 15 (Fig. 5). These groups returned to normal during the following fortnight.

*Platelets.* During the examination of stained blood smears rough estimates of platelet numbers were made. The only indications of a reduction in platelets were encountered 8 days after irradiation in the 400 rad neutron and roentgen groups and in some individuals of the 200 rad neutron group 6 and 9 days after irradiation.

*Reticulocytes.* Polychromatophilia of erythrocytes was used to estimate reticulocytes. Increased polychromatophilia was noted in smears from all irradiated groups in the range of 6 to 20 days after exposure.

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1 to 3 days. Recovery occurred in 6 to 20 days in all parameters excepting the lymphocyte counts. The RBE of 14 MeV neutrons under the experimental conditions appeared to approximate that of the used roentgen rays for the parameter studied


## ZUSAMMENFASSUNG

RF Mäuse wurden einer Dosis von 50 bis 100 rad 14 MeV Neutron-Bestrahlung oder einer Röntgenstrahlung von 100 bis 400 rad ausgesetzt, und die totalen und differentialen Leukozyten und Hämatokrit Werte wurden bestimmt. Es konnte eine Korrelation zwischen Leukopenie und Röntgendosis beobachtet werden, die innerhalb 1 bis 3 Tagen ihr Maximum erreichte. Die Genesung erfolgte nach 6 bis 20 Tagen in allen Parametern mit Ausnahme der Lymphozytenanzahl, Unter den gegebenen Versuchsbedingungen zeigte es sich, dass das RBÄ (radio-biologische Äquivalenz) der 14 MeV Neutron Bestrahlung dem der Röntgenbestrahlung des untersuchten Parameters nahekam.

## RÉSUMÉ

Des souris RF ont été exposées à des doses de neutrons de 14 MeV allant de 50 à 400 rad ou à des doses de rayons röntgen allant de 100 à 400 rad On a fait la numération et la formule leucocytaires ainsi que l hématocrite. On a observé une corrélation entre le leucopénie et la dose röntgen, qui est à son maximum entre le premier et le troisième jour Tous les paramètres reviennent à la normale en 6 à 20 jours, sauf le nombre des lymphocytes. Dans les conditions de cette expérience, le RBE des neutrons de 14 MeV paraît voisin de celui des rayons röntgen pour le paramètre étudié.


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to 10 years. The controls on the 77 subjects took place from 10 to 15 years from the time of therapy a control group of 106 untreated subjects were also examined.

Irradiation factors Siemens bomb apparatus fields 6 × 8 cm and 10 × 30 cm, FSD HVL 0.2 to 0.8 mm Cu mA 10 kV 120 to 160, dose rate 40 to 44 r/min irradiation mainly fractionated usually with doses of 10 r to 50 r to the surface at 1 to 2 day intervals the total surface doses being most frequently of the order of 125 r to 300 r The total doses when higher were administered in a greater number of courses with intervals of several weeks or months. The applicator was adjusted so that the area of cervical lymph node involvement was included. The thyroid gland, larynx, pharynx, cervical spine, mandible, clavicle and sternal manubrium were, according to the technique used, either in the direct beam of irradiation or in its vicinity It can be assumed that in children up to six months old the thymus was also directly irradiated, because at this age the gland is placed physiologically high up and reaches into the thoracic inlet (VALKER 1959)

With the irradiation technique used, a response in all tissues and organs of the irradiated area and an occasional general reaction were to be expected. The investigation was therefore divided into four main sections, each being carried out by the same members of the team throughout.

1 *Radiotherapeutic investigation.* Attention was directed to radiation changes in the skin, the other soft tissues of the neck, face and oral cavities. The history of the original condition was determined and any further exposure recorded.

2. *Ear nose and throat examination.* A complete ENT examination, including anterior and posterior rhinoscopy examination of the oral cavity throat and tonsils, indirect laryngoscopy and diaphanoscopy were performed phoniatric and histologic examinations were carried out where necessary

3 *Roentgen examination.* Examination of the cervical spine, mandible and larynx, and sometimes of the facial bones, teeth and thoracic inlet were also performed

4 *Pediatric examination.* The complete clinical examinations included basic biochemical values of the blood. The characteristics that are dependent in their development mainly on the functional influence of the endocrine glands within the irradiated area were followed. A search was also made for other signs that might reveal any condition resembling damage connected with irradiation.

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# DELAYED CHANGES IN THE GROWING ORGANISM FOLLOWING SMALL RADIATION DOSES

by

VL STASEK, J JAKOUBKOVÁ, J KOLÁR, K BRACHFELD ST TICHY M LOKAJICEK and VL. MALY

The study of delayed changes in the growing organism following small radiation doses may offer some new findings in the sphere of clinical radiobiology Some time ago a preliminary report was published (STASEK et coll. 1962) on the results of examining a group of children irradiated early in life for benign conditions This work has been continued and extended to include further irradiated children and a non irradiated control group The results of the examinations have been re-evaluated and an analysis of the material by a statistical method and dosimetric evaluation has been made The results are now presented.

*Material and Methods* The material consists of children irradiated during the period 1946 to 1951 for cervical lymphadenitis (72 cases) and hyperplasia of the thymus (5 cases) The ages at the time of treatment ranged from 2 months

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3 *Tumours* were diagnosed in 3 irradiated subjects, i. e in two adolescents 14 years after exposure and in one girl who died 8 1/2 years after irradiation for benign cervical lymphadenitis. Papilloma of the anterior palate arch was discovered in a 14-year-old girl and histologically confirmed as a benign papilloma. Carcinoma of the thyroid gland with metastases to the cervical lymph node was present in a 14-year-old boy An ovarian tumour was discovered in a 12-year-old girl and laparotomy revealed metastases in the abdominal organs and ascites. Seminoma of the ovarium teratogenic type, was histologically proved. Autopsy disclosed metastases in the pelvic and abdominal organs as well as in the spine.

*B The control group*

There were 106 subjects in the control group and, by the same examination method as was used for the irradiated group, 98 were found to be physically normal. Thinning of the cervical intervertebral disks of the cervical spine with no other changes in the skeleton, was present in 5 subjects. In 3 subjects, systemic disorders were found in two boys these consisted of an adiposogenital type of development and in one abnormal obesity distinctly marked in the area of the mammary glands.

## Evaluation of the findings

1 *Roentgen diagnosis* The search for and evaluation of radiation changes in bones had to be conducted over the entire area that might have been exposed to irradiation Decreased volume and flattening of the mandible, leading to asymmetry of the facial skeleton accompanied by slight structural changes in the cervical vertebrae was observed in 3 cases. No advanced spinal changes, such as belong to the higher degree of radiation damage to a growing spine (asymmetry and wedge-shaped deformation of the vertebrae with irregular contours and scoliosis) (SARRAZIN et coll. 1961) were evident in the irradiated group. Slight alteration in the bone structure of the vertebral bodies, accompanied by changes in the mandible were seen in 25 irradiated children. These structural changes appeared as hypertrophic porosis with accentuated width of the bone trabeculae, and with so-called growth lines, i e. fine dense strands, running transversally through the vertebrae parallel to their margins These appearances are manifestations of retardation of bone growth equalized at a later period this retardation is non-specific and usually accompanies all serious conditions of general ill health in children. Similar structural changes in the spine were not, however evident in the control group. A decrease in

## Results

### *A. The irradiated group*

Since the doses applied were low and the irradiation fractionated it was probable that delayed changes, if they appeared at all would be slight. Since changes of this type may have a non-specific character (DUNLAP 1957) it was necessary in evaluating the findings and in examining them critically from the viewpoint of causal connection to consider all pathogenic factors as well as the radiation exposure. The patients were accordingly divided into two main categories.

The first category consisted of subjects in a normal state of health. Those with pathologic conditions in whom a definite further pathogenic factor was present in addition to that of irradiation were also included. The findings in this category were marked negative.

The second category consisted of 45 subjects in whom pathologic conditions were diagnosed and no additional pathogenic factor could be determined. The findings in this category consisted of (1) changes in the tissues and organs within the irradiated area, (2) the presence of systemic disorders, and (3) evidence of tumours. These were marked positive.

1. *Changes in the tissues and organs within the irradiated area* were diagnosed in 41 subjects. An abnormal degree of dental decay with numerous periapical granulomas mostly affecting the lower jaw (in three), facial asymmetry with unilateral mandibular hypoplasia (in three), changes in the cervical spine (alteration of bone structure, thinning of the intervertebral discs, marginal osteophytes) (in 25 cases), definite atrophy of the mucous membranes of the pharynx and the laryngeal aperture combined with dryness of the mucous membranes and accompanying dilation of capillaries or groups of capillaries (in 23 cases), asymmetry of the larynx with normal functioning of the vocal cords (1 case).

2. *Systemic disorders were diagnosed in 14 subjects.* Dysmenorrhea in a 14-year-old girl, metrorrhagia in a 11 year-old girl, considerably delayed development of secondary sexual signs in a 19-year-old girl, hypogenitalism and subnormal general development in 3 boys, an adiposogenital type of development in 4 boys, in one connected with marked psychic retardation, obesity with premature development of secondary sexual signs in one boy, and gynecomastia in 3 boys, unilateral in one and bilateral in the other two.

changes were often present in unusual areas the epiglottis, pharyngoepiglottal folds and piriform sinuses. They were not found in the control group

Asymmetry of the larynx, with normal functioning of the vocal cords, was evident in one irradiated girl, and a papilloma on the anterior arch of the palate histologically confirmed as benign in another girl. These changes were additional to those mentioned above.

Chronic atrophy of the pharynx and respiratory tract lowers the protective resistance to various harmful influences likely to be encountered when these adolescents come into working conditions on reaching maturity or begin to smoke. Atrophic changes in the pharynx may after some years even affect the condition of the respiratory tract. The epithelium, glands and mucous capillaries and all their functions are damaged and future control examinations may give an indication of the eventual effects of the initial trauma.

3 *Clinical examination* The pediatric examination served as a basis for evaluating the influence of irradiation on the general development of the subjects, and because so many significant endocrine glands, e. g the thyroid, thymus and pituitary lay within the irradiated area it could be assumed that growth deviations would occur The situation is rendered more difficult as these three glands may exert a broad influence on development e. g psychic and sexual development, or indirectly guide more restricted fields of growth through their influence on the other endocrine glands. Most of these children were irradiated either as infants or toddlers whereas the examinations were carried out at times when the most complicated and unsettled period of development is to be expected, i. e puberty In view of the variability which characterizes the period of puberty in the broadest sense of the word the final evaluation of deviations was not easy

With one exception there was no family history of endocrine or psychic disturbances. Evaluation of general development was made according to the height and weight, which were compared with the Czechoslovak all-state norms ("Tables published by the Ministry of Health on the basis of a somatometrical investigation carried out by the Anthropological Commission, Prague 1951") Height was considered with due regard to age and weight, secondarily in relation to height, so that any somatic disproportion between height and weight was evident. The general development in the irradiated group did not differ from that in the control group. The chest and abdominal organs were either within physiologic limits, or the changes found could not be correlated with irradiation.

Biochemical data were recorded for blood proteins, non-protein nitrogen cholesterol sodium, potassium, calcium phosphorus, and alkaline phosphatase

the thickness of the intervertebral disks and structural changes were present in the irradiated group Five children of the control group however also had narrowed intervertebral disks so that this sign may not be of significance. At the same time it was noted that two of the irradiated children had osteophytes of the vertebral bodies posteriorly in the affected joints whereas these were absent in the control group

Calcification of the laryngeal cartilages became visible only after the age of 18 years There was no proof that this was more premature or marked in the irradiated than in the control group

2 *ENT diagnosis* The aim was to determine the condition of the mucous membrane of the oral cavity pharynx and larynx in the patients who had been irradiated in early childhood and in the control group The significance of the changes in relation to general health was considered

The ENT case histories revealed previous illnesses with their frequency and length of duration In evaluating the results of the examination the following were regarded as negative signs of focal infections with adenoidal vegetation, obstruction of the nares or chronic tonsillitis with pus or debris Adolescents with symptoms of acute inflammation of the respiratory tract who did not present themselves for examination after the conclusion of an attack, were included i e 9 subjects in the irradiated group In diagnosing the findings a satisfactory differentiation between changes caused by chronic or acute inflammation and those caused by radiation was found to be impossible because it was recognized that some of the changes produced by the latter may be similar to those that occur after tonsillectomy (thinning of the mucous membrane reduced moistness) the findings in the tonsillectomy patients were also considered negative Of the 33 tonsillectomy patients examined 15 belonged to the irradiated group and 18 to the control. The operation in the irradiated group had not been followed by haemorrhage, and healing had occurred within the normal period Thinning of the mucous membrane and reduced moistness of the throat was sometimes observed and occasionally dilation of the capillaries

Thinning of the mucous membrane of the pharynx or laryngeal aperture was evident in 15 subjects of the irradiated group and in some was accompanied by a reduction in its moistness These changes do not necessarily indicate delayed radiation changes as they may be found in non irradiated subjects as well they were present in 6 subjects of the control group

Twenty three adolescents of the irradiated group had marked thinning and atrophy of the mucous membrane of the pharynx or laryngeal aperture and an increase in the number of dilated capillaries or groups of capillaries. These

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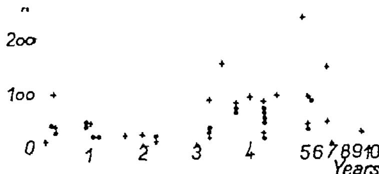



Fig. 2. Doses absorbed in the larynx area in individual cases, converted to equivalent single dose radiation. Positive finding + negative O

typical glandular disk formation was evident in the area of the nipples. Gynecomastia is known to occur commonly in endocrine disorders (TREVES 1958)

The most significant diagnosis was made in one boy. He had been subjected to irradiation for bilateral cervical lymphadenitis at the age of 3 and a total dose of 420 r fractionated over a period of 5 weeks, had been administered. At the age of 14 a cervical node was extirpated in which metastases of cancer of th thyroid gland were histologically verified. The tumour was mainly cystopapillary in structure, in parts containing macrofollicular formations with colloid, and in others a more microfollicular to solid formation. Subtotal strumectomy was also performed. Histologic examination revealed the tumour structure to be the same as the metastases. There were signs of endocrine stigmatisation — some obesity and premature development of secondary sexual signs. The boy is at present under treatment at the endocrinologic institute.

Two boys in the control group had evidence of an adiposogenital type of development, one of them in the form of abnormal obesity which was more strikingly marked in the chest, especially in the area of the breasts.

No characteristic signs of radiation damage were present in any of the subjects. Non-specific deviations, indicating endocrine unbalance were apparent, it is true, and of course radiation cannot be ignored as one of the possible etiopathogenetic factors. The supposition is admissible that the irradiation of endocrine glands in early childhood left a latent trace and later appeared in puberty as signs of endocrine unbalance. It was thought that a statistical mathematical evaluation of the frequency of the observed findings, and a dosimetrical analysis of the applied doses might help to clarify this question.

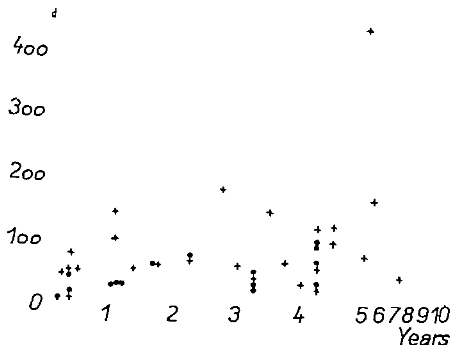



Fig 1 Doses absorbed in cervical spin area in individual cases, converted t equivalent singl dose radiation. Positive finding + negative C

The results corresponded to the medium values for the given ages. In so far as isolated minor deviations appeared they were not significant.

Fourteen subjects in the irradiated group presented evidence of greater or smaller deviations that could be explained by disturbed functioning of the endocrine system

Dysfunction of the glands controlling sexual development and secreting growth hormone was apparent in 3 girls. Assuming an etiopathogenetic dependence of the origin of these disturbances on radiation, then in two of the girls (dysmenorrhea, metrorrhagia) the effect could be considered rather as a stimulatory one and in the third girl (considerably delayed development of secondary sexual signs and general hypotrophy) as an inhibitory effect both as regards sexual maturing and the effect on growth.

The largest group consisted of 7 boys in whom delayed sexual development was diagnosed. Hypogenitalism accompanied by subnormal general development, i. e marked general hypotrophy was present in three of these, and the adiposogenital type of development was common to the other four boys, in one of them accompanied by marked psychic retardation.

Incidence of gynecomastia was demonstrable in 3 boys, unilateral in two and bilateral in one boy The nipples protruded and were broadly cone-shaped

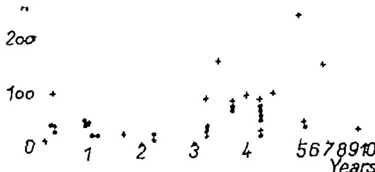



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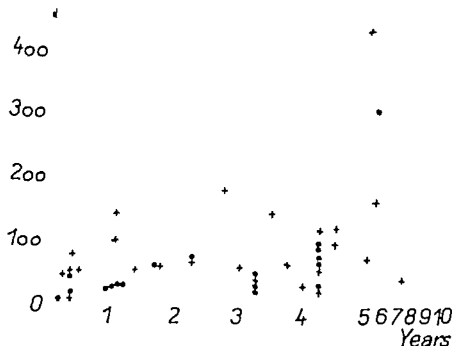



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Table 1

| Age group (years) | No. of irradiated children | Cervical spine | | | Larynx | | | Average volume dose rad cm³ | Percentage of children with system deviation | Frequency of system deviation per volume dose $10^4$ rad cm³ |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Average dose (rad) | Percentage of children with positive finding | Frequency of positive findings per dose 25 rad % | Average dose (rad) | Percentage of children with positive finding | Frequency of positive findings per dose 25 rad | | | |
| 0—1/2 | 7 | 52.3 | 37.1 | 44.2 | 35.3 | 42.8 | 30.4 | 17 650 | 71.4 | 40.4 |
| 1/2—1 | 7 | 16.7 | 14.3 | 21.4 | 44.7 | 14.3 | 8.0 | 30 700 | 28.6 | 9.3 |
| 1—2 | 15 | 63.3 | 26.7 | 10.5 | 54.6 | 26.6 | 12.2 | 14 100 | 0 | 0 |
| 2—3 | 11 | 68.6 | 27.3 | 10.0 | 58.5 | 9.1 | 3.9 | 22 500 | 9.1 | 4.0 |
| 3—4 | 10 | 59.1 | 40.0 | 16.9 | 58.5 | 50.0 | 21.3 | 15 800 | 10.0 | 6.5 |
| 4—5 | 13 | 98.0 | 53.8 | 13.9 | 69.1 | 30.8 | 11.1 | 36 300 | 18.2 | 5.0 |
| 5—10 | 14 | 101.2 | 14.3 | 3.5 | 74.2 | 35.7 | 12.0 | 42 000 | 14.3 | 3.4 |

a relation between the occurrence of the changes and the age at the time of exposure, and whether the biologic effect could be related to the applied dose.

The average absorbed dose in the cervical spine area and larynx was first determined in each child. It was also found useful to determine the volume dose. The surface doses and the irradiation technique used were considered for this purpose. In view of the considerable differences in the length and number of irradiation courses, it was also necessary to take into consideration the time factor. An equivalent absorbed dose was therefore calculated which should have the same biologic effect in single dose radiation. STRANDQVIST's (1944) nomogram was used. The equivalent absorbed doses in the cervical spine area and larynx in individual subjects, divided according to age, are shown in Figs 1 and 2. Fig. 3 gives the volume doses, which are also converted to single doses with the equivalent biologic effect. If the correctness of the linear dependence between the dose and biologic effect, expressed by the positive findings (BEACH et coll. 1962, HAMILTON 1963) be assumed, the question formulated at the beginning of this section may be answered. The data are collected in the Table.

The irradiated children were divided into 7 groups according to age at the time of exposure. An average equivalent dose and the frequency of positive findings in the cervical spine and larynx area were determined for each group. In assuming the proportionality the percentage of positive findings, corresponding to the equivalent absorbed dose of 25 rad was determined. The fre

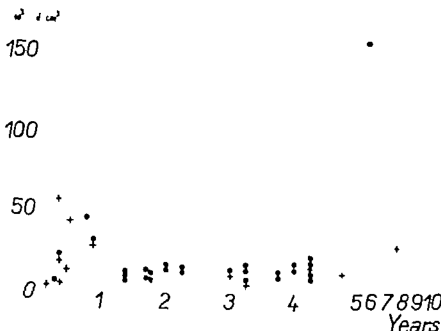



Fig 3 Volume doses in individual cases, converted to equivalent single dose radiation. System deviation + physiological finding ○

*Statistical analysis* The statistical evaluation was approached with the knowledge that it is impossible to find an ideal control group that would correspond to the irradiated group A random selection for the control group was therefore made The aim of the statistical evaluation was to discover whether the difference between the frequency of positive findings in the irradiated group and that of the control group was significant Although all types of verified findings, including some of the less numerous are contained in the records, only those occurring with a frequency capable of statistical treatment were admitted for analysis. Changes in the cervical spine and in the mucous membrane of pharynx as well as systemic disorders were present in the material

The statistical evaluation was carried out as follows a four fold table was worked out for each age group the exact value of P was calculated, and the values obtained were combined for all age groups with the help of the $\chi^2$-test It emerged that the difference in frequency of the three types of findings mentioned is statistically significant — for system deviations at a 5 per cent level and for cervical spine changes and mucous membrane changes at a one per cent level of significance

*Dosimetric analysis* The result of the statistical analysis led to an investigation of whether it would be possible to establish, at least in general terms

As with the local tissue and organ changes, systemic disorders were in the nature of non-specific disturbances probably referable to the endocrine glands. The thyroid, thymus and pituitary glands were in the direct beam of radiation or in its vicinity. These are endocrine glands that can exert a direct general influence on growth, e. g. on psychic and sexual development, or indirectly guide more restricted fields of development by influencing the other endocrine glands with which they are in correlation. Irradiation in the present material was carried out in early childhood, i. e. at the time when these glands were still for the most part quiescent. With the statistical significance — at the five per cent level — of systemic disorders it would be possible to assume that radiation had left latent traces of damage to the organs manifest at puberty.

The frequency of tumours in 3 subjects of the irradiated group (cancer of the thyroid gland, benign papilloma of the palate arch and an ovarian semi noma) is beyond the range of statistical evaluation and no conclusion can be drawn as to its relation to radiation as a pathogenic factor.

No clinical signs of radiation changes in the skin were found, although it was subjected to a higher radiation dose than the other organs. It may be possible to explain this by the fact that the skin of children possesses a greater reparative capacity than the other organs under consideration in the area of the neck.

*In view of the fact that the difference between the frequency of the tissue and organ changes and systemic disorders in the irradiated group and that of the control group was statistically significant, or very significant, it is assumed that radiation acted as an important pathogenic factor. Even small doses of radiation are undoubtedly not harmless for the growing organism. The authors therefore consider that it would be advisable to revise from this point of view the use of ionizing radiation in the treatment of benign conditions in children and adolescents.*

**Acknowledgements**

The authors wish to express their thanks to Mrs A. Nebremská and Mrs G. Tráilinová for their valuable technical assistance.

## SUMMARY

A group of 77 subjects irradiated in early childhood for benign conditions were examined 10 to 15 years later, a group of 106 patients acting as control. In view of the fact that the difference between the frequency of tissue and organ changes and systemic disorders in the irradiated group and that of the control group was statistically significant or very significant, it is assumed that radiation acted as an important pathogenic factor.

quency of systemic disorders corresponding to the equivalent dose of $10^4$ rad $cm^2$ was similarly calculated

The results reveal that in children irradiated before they reach the age of one year the frequency *of positive findings or of systemic deviations was, for* the same dose, considerably higher than in older children The values shown in the Table even indicate that in children under one year of age the frequency of findings indicates a marked increase with decreasing age

As to the second question it may be assumed that from the material it may be possible to find at least a general relation between the absorbed dose and the frequency of the findings in the cervical spine and laryngeal area The question demands a separate theoretical and detailed statistical study

## Conclusions

A group of 77 children irradiated in early childhood for benign conditions were examined 10 to 15 years after exposure A control group of 106 children and adolescents was also examined Local changes in the tissues and organs and systemic disorders were revealed in both groups and tumours were also discovered in the irradiated group

Changes in the cervical spine were characterized in the irradiated group by alteration in the bone structure of the vertebral bodies, signs of osteophytes posteriorly and diminution in the thickness of the intervertebral disks. These changes accompany all more serious disturbances leading to temporarily retarded growth in children and are therefore non specific. Only degeneration of the intervertebral disks in the area of the cervical spine was found in 5 adolescents of the control group

More marked changes in the irradiated group were observed in the lower jaw These appeared as a decrease in size and unilateral flattening of the mandible which led to facial asymmetry They were accompanied by abnormal dental decay *and the formation of periapical granulomas.*

Thinning of the mucous membrane of the pharynx and laryngeal aperture combined with reduced moistness may be observed in those who have not been exposed to irradiation It is, however considerably rarer in young subjects than in adults. In 23 subjects of the present series who were exposed to radiation the condition was especially marked for in addition to atrophy and dryness of the mucous membrane, capillaries, or groups of capillaries were found *to be dilated These lay not only in the pharynx* but also in the epiglottis, pharyngoepiglottical folds, valleculae and piriform sinuses. These changes did not occur in the control group

The difference in the frequency of all the findings in the two groups was significant statistically i e at a one per cent level of significance

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# EFFECT OF 5-HYDROXYTRYPTAMINE AND CYPROHEPTADINE ON TUMOUR BLOOD FLOW

## Estimation by rate of cooling after microwave diathermy

by

DONALD B. CATER, ANN PETRIE and D. ANNE WATKINSON

The radioprotector 5-hydroxytryptamine (5-HT) was found to reduce the oxygen tension in tumours more rapidly than the oxygen tension of bone marrow (CATER, GRIGSON & WATKINSON 1962). After 5-HT the oxygen tension in tumour does not rise during inhalation of oxygen at atmospheric pressure or even at a pressure of 3 atmospheres absolute (CATER, SCHOENIGER & WATKINSON 1962, 1963). The 5-HT effect was reversed or prevented by the anti-histamine anti-5-HT drug cyproheptadine. A reasonable interpretation of these findings was that 5-HT produced a considerable degree of circulatory stasis in the tumour.

It is important to collect evidence for or against a special relationship of 5-HT to tumour circulation because some observers have suggested that 5-HT assists the implantation and spread of tumour cells (SCOTT, SCHELLING & STONE 1958, SCOTT & STONE 1959, CONVALIUS 1960, CONVALIUS, HOWARD & STRAWITZ 1963) and is involved in the reaction to carcinogens (COUPLAND &

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## ZUSAMMENFASSUNG

*Eine Gruppe von 77 Personen, die im frühen Kindesalter für gutartige Erkrankungen* röntgenbestrahlt worden waren, wurden 10 bis 15 Jahre später untersucht, eine Gruppe von 106 Personen diente zum Vergleich. In Anbetracht der Tatsache, dass Gewebe- und Organveränderungen und Systemerkrankungen nach Bestrahlung in statistisch bedeutsamer Weise häufiger gefunden wurden als bei der Kontrollgruppe, *muss angenommen werden, dass* Bestrahlung ein wichtiger pathogener Faktor ist.

## RÉSUMÉ

Un groupe de 77 sujets irradiés dans leur jeune enfance pour des affections bénignes ont été examinés 10 à 15 ans plus tard et comparés à un groupe de 106 sujets témoins. Étant donné que la différence entre la fréquence des lésions de tissus et d'organes et les troubles *systémiques chez les sujets irradiés et chez les sujets témoins est statistiquement significative* ou très significative, les auteurs admettent que l'irradiation a eu un rôle pathogénique important.

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soldering this at the pointed end of the needle. These thermocouples were inserted into the tumour so that they were parallel with the horizontal axis of the mouth of the wave guide. The other junctions of the thermocouples were insulated and placed in a constant-temperature water bath held at 37° C. The thermocouple currents were measured by two (Cambridge Instrument Co) spot galvanometers shunted by suitable resistances. The thermocouples were calibrated frequently and remained constant. Experiments with water phantoms and living and dead tissues indicated that power was not picked up by the thermocouples direct from the microwave beam, even at considerably greater power outputs than were used in the experiments.

In the experiments of the first series, the temperature of the tumour was recorded and then the tumour was heated to 40 or 41° C for 1 min, the diathermy turned off and the fall of temperature followed for some minutes. This procedure was repeated and gave normal runs 1 and 2 ($N_1$, $N_2$). 5-HT 5 mg/kg (of base) was injected intraperitoneally and after 10 min the heating cooling cycle was repeated. Observations were made on another cycle of heating and cooling 20 to 30 min after the injection of 5-HT ($S_1$ and $S_2$). Cyproheptadine, 2 mg/kg was then injected intravenously (occasionally 4 mg/kg intraperitoneally) and after an interval of 10 min two more heating and cooling cycles were observed ($C_1$ and $C_2$). The rectal temperature was noted and this was kept as constant as possible. The animal was killed with $CHCl_3$, and the tumour dissected to assess the state of the tumour in which the thermocouples were situated.

In a second series of experiments (because the heating cycle might be damaging the tumour and producing 5-HT and histamine) only one heating cooling cycle was used for each type of treatment and the temperature was raised only to 40° C. Occasionally a second dose of cyproheptadine was injected followed by an additional cycle of observations. Heating and cooling curves were also observed after death.

In a third series of experiments after one cycle, the effect of noradrenaline 50 μg/mg S.C. was studied and then 5-HT and cyproheptadine.

A fourth series of experiments was made on the spontaneous mammary carcinomas in mice. The mice were too small to make it easy to suspend the tumour in the microwave beam, and the tumours were frequently in sites which made this difficult. The results were rather unsatisfactory because several times the thermocouples were found to be in fluid-filled cysts in the tumours.

In a fifth series of experiments, using rats, after two control cycles, cyproheptadine was given and the effect studied before 5-HT was given in order to ascertain whether cyproheptadine would block the effect of 5-HT.

RILEY 1960, CSABA, HORVATH & MOLD 1961) CRILL (1963) has suggested that the therapeutic effect of heat on tumours can be increased by 5 HT

A knowledge of tumour blood flow is important in radiotherapy because of the oxygen effect and in chemotherapy because access of the therapeutic agent to the tumour cells is dependent upon blood flow In fact certain therapeutic agents are thought to destroy a tumour by damaging its vessels (e g the polysaccharide of SHEAR 1941 SHEAR & PERRAULT 1944) Tumour vessels are known to be abnormal in arrangement and structure a deeper knowledge of their anatomical peculiarities, and of their function might facilitate new ways of therapeutic attack upon cancer through this Achilles heel of tumour organisation

During a study of tumour therapy with combined microwave heating and radiation (CATER, SILVER & WATKINSON 1964) a technique was developed for following the tissue temperature of the tumour even during the microwave heating by the aid of very fine thermocouples It was argued that after the temperature of a tumour in the leg of an animal had been raised by 3 or 4 C above rectal temperature the rate of cooling (apart from the effect of metabolism) would depend partly on cooling through the skin to the ambient partly on conduction from the heated leg to the cooler body and partly on cooling of the heated tumour by its blood flow It was further argued that if injection of 5-HT markedly reduced tumour blood flow then the rate of cooling of the tumour after its temperature had been raised to 40 or 41 C by microwave heating would be slower after 5 HT and it should be possible given the right conditions to reverse this effect with the anti histamine anti 5-HT drug cyproheptadine

## Materials and Methods

All rats had tumours implanted in the left leg The material included August strain rats with hepatoma 223 and white Wistar rats with Jensen sarcoma or Yoshida carcinoma A few C+ mice with spontaneous mammary carcinomas were also used

The animals were anaesthetised with 25 % w/v urethane 0 6 ml/100 g body weight The tumour bearing leg was suspended by an adhesive plaster stocking at the mouth of the wave guide of the 10 cm microwave diathermy apparatus (PERKINS 1955) The animal lay on its side and its body was out of the beam. The rectal temperature was taken by a fine mercury thermometer Two thermocouples were made of 0 5 mm diameter stainless steel, hypodermic dental needles by threading insulated constantan wire through the needle and

Eq (2) implies that the cooling curves have the form

$$T = A + \exp\ (-\beta t + C) \tag{5}$$

where $A = a/\beta$ and $C$ is a constant depending on where the time origin is taken.

In other words if the correct value for $A$ is chosen, then the logarithm of $(T - A)$ plotted against time is a straight line of slope $-\beta$. The value of $\beta$ may be estimated for each cooling run by fitting curves of the type represented by eq (5) to the experimental data. If $K$ $K_p$, $K_b$, and $m$ can be assumed to be constant for two cooling runs (on the same rat) then differences between values of $\beta$ for these two runs will be proportional to differences in blood flow. $A = a/\beta$ may also be expected to change with blood flow but the value of $A$ is in fact much less sensitive to change in blood flow than the value of $\beta$.

The basis of the analysis was that changes in the estimated values of $\beta$ (which are of course subject to some degree of variation) correspond to changes in blood flow although no attempt was made to estimate this flow. $\beta$ was estimated for each cooling run and the results interpreted in terms of blood flow.

## Results

If one attempts to estimate $\beta$ by plotting log $(T - A)$ against time, the slope, $-\beta$ of the line is dependent on a proper choice of the value $A$. For this reason the best curve of the theoretical type was fitted to the experimental data by the method of least squares. The values of $A$, $\beta$ and $C$, were so chosen that the sum of the squares of the expression $(T - A - \exp\ (-\beta t + C))$ over all the experimental points $(T\ t)$ was as small as possible. A considerable amount of computation is involved in the fitting of this model by least squares. Suitable programmes were therefore developed and the computation was carried out on the Cambridge University electronic computer EDSAC. The value of the minimized sum of squares was found to agree well with that which could be expected on the basis of the experimental error in reading the instruments. In the majority of cases, $A$ was found to be very near to rectal temperature (usually one or two degrees below).

Post mortem examination occasionally showed that the end of a thermocouple did not lie in the tumour. Observations made on such thermocouples were discarded from the analysis. In cases where both thermocouples lay in tumour the behaviour of the estimated values of $\beta$ was remarkably similar. Indeed, this was to be expected, and had there been no correlation between the pair of thermocouples in one tumour the validity of the results would have been open to grave doubt. Due note of this correlation had to be taken when calculating standard errors of the mean response to the various treatments.

## Theoretical considerations

If we consider 1 cm of tissue surrounding the tip of the thermocouple, after being heated to temperature $T$ this will lose heat as a result of cooling by the blood It will also lose heat by conduction down the limb and through the skin but will gain heat as a result of its metabolic activity

A strict mathematical analysis of the situation is not possible but assuming that the amount of heat gained by the blood flowing through the test volume of tissue is proportional to the total amount of heat gained by this blood during its journey from the arteries to the tissue then the rate of loss of heat due to cooling by the blood will be equal to

$$k_1 S_b f(T)\ (T - T\ )$$

where $S_b$ equals the specific heat of the blood $f(T)$ is the rate of flow of the blood in g/cm³/min at temperature $T$ $T$ is rectal temperature and $k$ is a constant of proportionality The rate of loss of heat down the limb will be approximately equal to $K_2(T - T\ )$ where $K_2$ is a constant depending on the conductivity of the limb and the rate of loss of heat through the skin will be equal to $K_3(T - T_a)$ where $k$ is a combined conduction and radiation constant and $T$ is a measure of the mean ambient temperature The rate of gain of heat will be equal to $m(T)$ where $m(T)$ is the metabolic rate expressed as cal/cm³/min

Since the rate of cooling of a volume of tissue is equal to its rate of loss of heat divided by its thermal capacity we can combine the results above into the following differential equation.

$$-\frac{dT}{dt} = \frac{1}{S}\left(K\ S_b f(T)(T - T\ ) + K_2(T - T\ ) + K_3(T - T_a) - m(T)\right) \qquad (1)$$

where $t$ represents time and $S$ is the thermal capacity of 1 cm of tissue. (It should be noted that $\frac{dT}{dt}$ means rate of increase of temperature with time )

If one assumes that the rate of blood flow and metabolism are independent of temperature and equal to $f$ and $m$ respectively (see *discussion*) eq (1) may be written more conveniently

$$\frac{dT}{dt} = a - \beta T \qquad (2)$$

$$\text{where } a = (K\ S_b f\ T + K_2 T + K\ T + m)/S \qquad (3)$$

$$\text{and } \beta = (k_1\ S_b f + K_2 + K_3)/S \qquad (4)$$

both being positive constants and $\beta$ may be referred to as the temperature-dependent rate of cooling

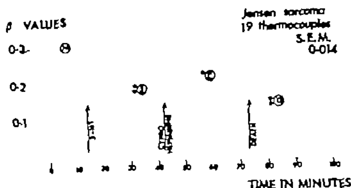



Fig. 2. Experimental series 2. Mean values of $\beta$, plotted against time, for Jensen sarcoma. One heating-cooling cycle for each treatment. D indicates cooling after death.

animals and thermocouples, and differs from that to be used when comparing repeated experiments using different animals and thermocouples. The mean for each run has been given the same standard error which is a pooled estimate based on all the cooling runs. There was no evidence that the standard errors varied significantly within an experimental series.)

The experimental results are presented graphically the mean value of $\beta$ i. e. $\bar{\beta}$ for a particular cooling cycle is plotted against the mean of the times at which the cooling cycle was carried out. Examination of the results however showed the change in the value of $\bar{\beta}$, from one cooling cycle to the next, did not depend on the time between them. The mean value of $\beta$ for each cycle is surrounded by a circle of radius equal to the standard error of the mean.

*Experimental series 1 two cycles of heating and cooling for each treatment.* The results are summarized in Fig 1 in which the mean values of $\beta$ (temperature dependent rate of cooling) for Yoshida carcinoma, Jensen sarcoma and hepatoma 223 are plotted against time. The different heating-cooling cycles are indicated as follows with no treatment N and N after 5-HT $S_1$ and $S_2$ after the anti 5-HT drug cyproheptadine $C_1$ and $C_2$. The size of the circle indicates the standard error of the mean in the vertical direction. When the mean values of $\beta$ are significantly different, at the 5 % level, from the preceding value, assuming the direction of change has been predicted, one asterisk is placed against it. Two asterisks indicate that the difference is significant, at the 5 % level when no assumptions regarding the expected direction of the change have been made. In Yoshida carcinoma (7 pairs of thermocouples) and hepatoma (7 pairs and 2 single thermocouples) there was a significant fall of $\beta$ after injection of 5-HT and a rise of $\beta$ after injection of the anti

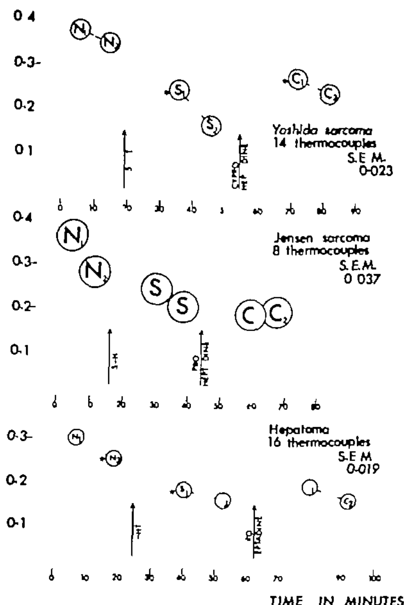



Fig 1 Experiment 1 series 1 The mea values of $\beta$ (temperature-dependent rat of cooling) for Yoshida carcinoma Jensen sarcoma and hepat ma 223 plotted against time N and N indicate control heating nd cooling S and S represent values after admi istrati of 5-HT while $C_1$ and $C_2$ re val es after cyproheptadi

Within each experimental series the results from different types of tumour were analysed separately and for each cooling cycle the mean value of $\beta$ together with its standard error were calculated (The standard error quoted is that to be used when comparing repeated experiments using the same

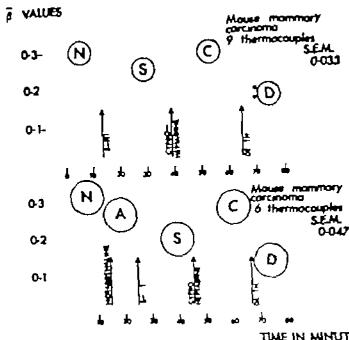



Fig 4 Experimental series 4 Mean values of $\beta$ in spontaneous mammary carcinoma in mice. The symbols denote the same as in previous figures.

In both cases, there was a rise of $\bar{\beta}$ after noradrenaline, and a significant fall of $\beta$ after 5-HT then a slight rise of $\beta$ after cyproheptadine, and a fall after death. Noradrenaline would be expected to have only a transient effect, and it will be seen that the subsequent changes of $\beta$ follow the same pattern of behaviour as in the experimental series 2 The values of $\bar{\beta}$ for the hepatoma were low this can probably be explained by its very poor circulation.

*Experimental series 4 with spontaneous mammary carcinomas in mice* The results are summarized in Fig 4 One series of mice (one single and 4 pairs of thermocouples) underwent the same sequence of treatment as in experimental series 2. The mean value of $\beta$ follows the same pattern as previously Another series of mice (3 pairs of thermocouples) underwent the same sequence of treatments as in experimental series 3 Excepting a fall in $\bar{\beta}$ between the normal and noradrenaline run, the results are the same as previously The tumours concerned in this experiment were however large, and approximately half the thermocouples were found to be in a cyst, a blood clot or near to the capsule of the tumour

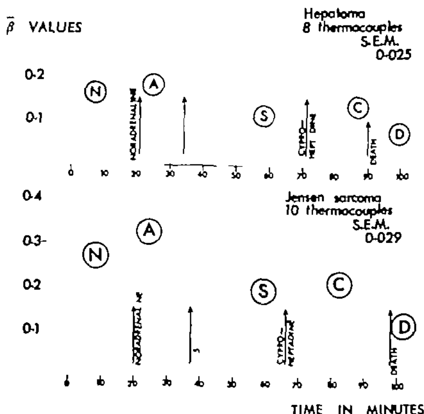



Fig 3 Experimental series 3 Mean values of $\bar{\beta}$ plotted against time for hepatoma and Jensen sarcoma In this series, the control cycle denoted N was followed by injection of noradrenaline denoted with A.

5 HT drug cyproheptadine This rise was significant in the Yoshida carcinoma In Jensen sarcoma the values of $\bar{\beta}$ show a general drift downwards except for C, but the number of thermocouples (4 pairs) were too few for the changes to be of statistical significance

*Experimental series 2 one heating-cooling cycle for each treatment* The results in Jensen sarcoma (1 single and 9 pairs of thermocouples) are given in Fig 2 The mean value of $\beta$ is significantly lowered after 5-HT and raised after cyproheptadine After death there is a significant fall in the mean value of $\beta$

*Experimental series 3 with noradrenaline as one of the treatments* These experiments were similar to those of series 2 except that after the normal cycle noradrenaline 50 µg/kg was injected subcutaneously and immediately afterwards the heating cycle was begun The results are summarized in Fig 3 for hepatoma (4 pairs of thermocouples) and Jensen sarcoma (5 pairs of thermocouples)

scored under the heading ++ If one thermocouple showed an increase and one a decrease in $\beta$ 1 was scored under +— The results of the 1st experimental series scored in this way are recorded in Table 1 and in Table 2 the results of the experimental series 2 to 4

Neglecting pairs of thermocouples for which the difference is of opposite sign, if $\beta$ is as likely to increase as to decrease between consecutive runs (this would happen for instance if differences in $\beta$ corresponded to random variation) then one would expect equal numbers of pairs of thermocouples to score (++) or (——) On this hypothesis, the probability of the observed result, or a more extreme result, can be calculated, and this is the figure given at the foot of each column of the table. A 'more extreme result is one in which the ratio of pairs of thermocouples scoring (++) to those scoring (——) is greater if the observed ratio is greater than 1 and smaller if the observed ratio is less than 1

Examination of the two tables showed that, with exception of the difference between a normal and a noradrenaline cycle these probabilities are all less than 0 05 the largest being 0.0385 and the results are consequently significant at the 5 % level. One can conclude that $\beta$ is more likely to go down than to go up between successive treatments except after cyproheptadine, when $\beta$ shows a highly significant tendency to increase.

## Discussion

### *Critique of the theoretical assumptions*

*Constancy of blood flow and metabolic rate* It is quite possible that the metabolic rate of the tumour might rise with temperature and that this would induce increased blood flow If this were the case, then eq (1) for the rate of cooling would not reduce to eq (2) with $\alpha$ and $\beta$ constant. The extremely good fit to the experimental data of the curve given in eq (5) indicates that for all practical purposes the rate of cooling has the form given by eq (2) This implies, to a first approximation at least, that variations in the blood flow and metabolism during a cooling run can be neglected.

*Constancy of K between different cooling cycles* This has been tacitly assumed in our comparison of $\beta$ from one cooling cycle to another This is a fairly reasonable assumption but there is no obvious means of checking it experimentally

*Constancy of K between different cooling cycles* $K$ is a constant depending on the conductivity of the limb, and it would not be expected to change between cooling cycles. However in approximating the rate of loss of heat up the limb by $K(T-T_r)$ a uniform temperature gradient was assumed. This might not

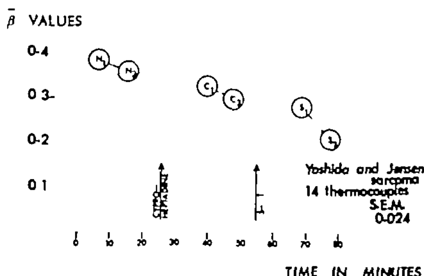



Fig 5 Experimental series 5 Mean values of $\beta$ i Yoshida carcinoma nd Jensen sarcoma i rats. The cyproheptadine was given before the 5-HT in this series there is a tendency fo $\beta$ to fall during the course of the experiments, and the cyproheptadine has not prevented th fall of $\beta$ in th second 5-HT cycle denoted $S_{2}$ (The tech ique used in these early experiments of heating the t mour to 41 C, and having two heating-cooli g cycles f each treatment was not good and may be partly responsible for th progressive failure of t mour blood flow )

*Experimental series 5 in which cyproheptadine was given before 5-hydroxytryptamine* There were two cycles of heating and cooling after each treatment The results are summarized in Fig 5 It is seen that $\bar{\beta}$ falls throughout the experiment The experiments of series 5 like those of series 1 belong to the earlier part of the investigation in which the temperature of the tumour was raised to 41 C during the heating cycle

*Combined analysis of experiments 1 to 4* Examination of the results of the various experimental series shows that while the direction of the change in $\bar{\beta}$ after a particular treatment is the same the magnitude of this change is not always so Therefore in order to combine results from different experimental series only the direction of changes in $\bar{\beta}$ were taken into account

Thermocouples in the same tumour behave very similarly Results were therefore considered in terms of pairs of thermocouples, and only tumours with readings from two thermocouples were included in this combined analysis. Observations were scored as follows. If in the run after a certain treatment both thermocouples showed a decrease in $\beta$ i e a decrease in blood flow compared with the preceding run the observation was scored 1 under the heading —— If both thermocouples showed an increase in $\beta$ 1 was

T bl 1 (*cont.*)

*tumours in which one or both thermocouples measured a decrease or increase in β (indicating change between successive runs*

| $S_1$ and $S_2$ | | | Anti-5-HT $S_2$ and $C_1$ | | | $C_1$ and $C_2$ | | | Number of pairs of thermocouples |
|---|---|---|---|---|---|---|---|---|---|
| −− | −+ | ++ | −− | −+ | ++ | −− | −+ | ++ | |
| 4 | 3 | 0 | 0 | 1 | 6 | 5 | 2 | 0 | 7 |
| 3 | 0 | 1 | 3 | 0 | 1 | 1 | 0 | 3 | 4 |
| 5 | 0 | 2 | 0 | 2 | 5 | 6 | 0 | 1 | 7 |
| 12 | 3 | 3 | 3 | 3 | 12 | 12 | 2 | 4 | 18 |
| $p = 0.0176$ | | | $p = 0.0176$ | | | $p = 0.0361$ | | | |

because the precise time when the power was cut off from the beam was uncertain If there was by chance any pick up of power out of the beam by the thermocouples, this artefact would have disappeared during the first half minute Also during the first half minute when temperature was changing rapidly small inaccuracies in timing would be relatively important.

In spite of all these theoretical and experimental difficulties significant results were obtained, indicating that a reduction in tumour blood flow occurred after the tumour had been heated, and after injection of 5-HT but that cyproheptadine (an antihistamine, anti 5-HT agent) increased the tumour blood flow

*Difficulties inherent in measuring tumour blood flow*

A more serious criticism of the technique used in these experiments for measuring changes in tumour blood flow is that it is indirect and time-consuming With such criticism the authors would be the first to agree were it not for the fact that all other methods at present available for measuring tumour blood flow are either indirect, time-consuming, inaccurate, or of limited application.

*Injection techniques* during life will show the anatomy of the vessels but only with great difficulty can information about the physiologic control of tumour vessels be obtained by such methods. Tumour vascular patterns have been extensively investigated by roentgen arteriography but the technique has been used for diagnosis rather than for the investigation of the functions of tumour vessels. For example, DOS SANTOS (1950) studied bone tumours by

**Table 1**

*Experimental series 1 Combined results for all tumours with 2 thermocouples showing the number of*
*of blood flow) be-*

| Treatment between runs: | Control N and N | | | 5-HT N and S | | |
|---|---|---|---|---|---|---|
| Change in $\beta$ (blood flow): | $--$ | $-+$ | $++$ | $--$ | $-+$ | $++$ |
| *Type of tumour* | | | | | | |
| Yoshida | 5 | 2 | 0 | 5 | 0 | 2 |
| Jensen | 4 | 0 | 0 | 2 | 0 | 2 |
| Hepatoma | 6 | 0 | 1 | 5 | 2 | 0 |
| Total | 15 | 2 | 1 | 12 | 2 | 4 |
| Probability of the observed or more extreme ratio of $(--)$ to $(++)$ | $p = 0.003$ | | | $p = 0.0381$ | | |

be the case, and the temperature gradient might well be affected by the blood flow This difficulty can be surmounted and still leave eq (1) and hence eqs (2)—(4) in the same form if instead of assuming that $k_2$ is constant we assume that $k_2$ depends on the blood flow $f$ Differences in $\beta$ (eq 4) will still reflect changes in blood flow but not in such a simple manner as previously

*Constancy of $k_2$ between experimental runs* The same remarks as given under the preceding heading apply also here

*The spatial resolution of the thermocouples was poor* Tests indicated that 3 mm of the tip was the zone of most rapid response but when this zone was in pus or blood clot $\beta$ still showed some change with treatment This was probably because the cooling of such a pool although it had no blood flow was dependent on the blood flow of the surrounding tissue Some conduction would also occur along the thermocouple so that the rate of cooling would be affected to some extent by the temperature of tissue surrounding the rest of its inserted length

The *cooling by blood flow* was responsible for only a part of $\beta$ If the other part, due to conduction from the hot limb to the body and the heat loss from the skin to the surroundings was large compared with the cooling by blood flow then changes in blood flow might be lost in random variations due to inaccuracies in the determination of the value of $\beta$ It should be noted that $\bar{\beta}$ was not equal to zero after death (see Figs 2 and 3)

*Readings of temperature* Those made during the first half minute after switching the power off the magnetron were discarded from the analysis. This was done

development and physiologic responses of the blood vessels of transplanted tumours (IDE, BAKER & WARREN 1939 ALGIRE & CHALKLEY 1945 ALGIRE & LEGALLAIS 1949 ALGIRE, CHALKLEY & LEGALLAIS 1951 NATADZE 1959) KERN & ZANDER (1959) watched the development of vessels in tumours induced by methylcholanthrene in the transparent tissues of the ear of the mouse. Again, the measurement of blood flow is indirect and the techniques are of restricted application.

The same may be said of estimations of blood flow by observing changes of skin temperature in superficial tumours (BIERMAN GILFILLAN KELLY KUZMA & NOBLE 1952 NATADZE 1959)

The oxygen cathode technique has also been used to get an indirect estimate of changes in tumour blood flow URBACH & NOELL (1958) explained the different response of squamous cell carcinoma and malignant melanoma of the skin to a test period of oxygen inhalation in terms of the known differences in the vessels of these two types of tumour CATER, GRIGSON & WATKINSON (1962) and CATER, SCHOENIGER & WATKINSON (1962 1963) used the oxygen inhalation test during tumour oxygen tension measurements as an indication that tumour blood flow was reduced after the injection of 5-HT CALIGARA & ROOTH (1961) have given formulas for calculating capillary blood flow from the rate of change of arterial $P_O$ compared with tissue $P_O$ when the subject breathes oxygen and KUMLIN ERTAMA MATTILA & HALONEN (1962) investigated the blood flow in muscles by noting the time when the muscle $P_{O_2}$ rose, following release of a cuff which had occluded the circulation in the leg for 8 minutes. KOLSTAD (1963) has measured tissue $P_{O_2}$ and capillary blood $P_{O_2}$ in carcinoma of the cervix, and correlated this with the intercapillary distance measured by colpomicroscopy

The heated thermocouple principle has been used for measuring changes of blood flow in tissue, and the difficulties have been reviewed by BILL (1962) but absolute measurements of blood flow can only be obtained under special conditions which would be difficult or impossible to attain in tumours.

Finally direct measurements of blood flow through transplanted tumours have been made by GULLINO & GRANTHAM (1961 1962) They injected the tumour into the ovary or kidney of rats and wrapped the organ in a paraffin envelope so that the tumour had a single vascular pedicle. Their technique enabled them to measure the tumour venous outflow directly and to investigate the effects of temperature, adrenaline and acetyl $\beta$ methylcholine upon the tumour blood flow This valuable technique can only be used with transplantable tumours in experimental animals and is open to the criticism that a spontaneous tumour often develops an extensive collateral circulation from adhesions with adjacent organs and structures.

Table 2

*Experimental series 2 to 4 Combined results for all tumours with 2 thermocouples showing the number of tumours in which one or both thermocouples measured a decrease or increase in β (indicating change of blood flow) between successive runs*

| Treatment between runs | Noradrenaline N and A | | | 5-HT A and S | | | 5-HT N and S | | | Anti 5-HT S and C | | | N of pairs of thermocouples |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Change in β (blood flow): | −− | −+ | ++ | −− | −+ | ++ | −− | −+ | ++ | −− | −+ | ++ | |
| *Exp. series 2* Jensen sarcoma | | | | | | | 9 | 0 | 0 | 1 | 2 | 6 | 9 |
| *Exp. series 3* Hepatoma | 2 | 1 | 1 | 3 | 1 | 0 | | | | 0 | 2 | 2 | 4 |
| *Exp. series 3* Jensen sarcoma | 1 | 0 | 4 | 4 | 1 | 0 | | | | 1 | 1 | 3 | 5 |
| Exp. series 4 Mammary *carcinoma* mouse | | | | | | | 2 | 2 | 0 | 1 | 1 | 2 | 4 |
| Exp series 4 Mammary carcinoma mouse | 1 | 0 | 2 | 2 | 1 | 0 | | | | 0 | 0 | 3 | 3 |
| Total | 4 | 1 | 7 | 9 | 3 | 0 | 11 | 2 | 0 | 3 | 6 | 16 | 25 |
| Probability of the observed or more *extreme ratio of* (−−) to (++) | p = 0.2744 | | | p = 0.0020 | | | p = 0.0005 | | | p = 0.0022 | | | |

radiographic arteriography using Thorotrast and BIERMAN BYRON KELLY & GRADY (1951) studied hepatic tumours Intra arterial injections of fluorescein will outline a superficial vascular neoplasm when the patient is viewed with ultra violet light (BIERMAN KELLY DOD & BYRON, 1950 BELLMAN 1953) Intravenous injections of lissamine green have been used in rats and mice by GOLDACRE & SYLVÉN (1959) and in mice, rats dogs and cats by OWEN (1960) GOLDACRE & SYLVÉN (1962) have reviewed the results obtained by injection techniques. An injection technique using radioisotopes can be used for a study of tumour blood flow (SAPIRSTEIN 1958 CATALAND COHEN & SAPIRSTEIN 1962) but this is neither simple and direct nor of wide application.

Transparent chamber techniques have been used to study the anatomy

Toxic absorption from dead cells also sets a limit to the rate at which it is safe to destroy a large tumour. In fact, one of the best features of radiation is that it kills cells slowly, and an important feature of surgical excision of tumours is that it removes the dead tissue from the body.

The tumour circulation is a weak link in the organisation of the tumour and it may be possible to exploit this weakness in cancer therapy. The bacterial polysaccharide, purified by SHEAR and his associates, would appear to work by damaging the vessels and causing haemorrhages in tumour. (It is noteworthy that it is much more toxic to the tumour-bearing than to the normal animal (SHEAR 1941; SHEAR & PERRAULT 1944).) Unfortunately the peripheral portions of the tumours often survived and the tumours regrew. The special absorption of certain drugs in tumours may be due to slow blood flow through tumours or may be increased by this. The action of heat may be greater on tumours because of poor blood flow (CATER, SILVER & WATKINSON 1964). This action of heat is increased by 5-HT (CRILE 1963). In general, agents which cause low blood pressure, or damage endothelium, or increase the inflammatory reaction, will tend to retard the blood flow and tend to cause haemorrhages or thromboses and necrosis in tumours. Deliberate attempts to kill anoxic tumour cells by such methods have obvious dangers with large tumours, but with more knowledge of the physiologic aspects of tumour vascularity it might be possible to exploit these methods in radiotherapy. The evidence presented in this paper that heat or 5-HT can reduce tumour blood flow, and that the effect of the latter can be reversed by the anti 5-HT anti-histamine agent cyproheptadine, may be useful in this respect.


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## SUMMARY

Cooling curves of transplanted rat tumours and spontaneous mammary carcinoma in mice, obtained after heating the tumours by 10 cm microwave diathermy, were subjected to mathematical and computer analysis. A formula was devised which accurately fitted the experimental results. Changes in the temperature-dependent rate of cooling were interpreted in terms of changes in tumour blood flow. Heating of the tumour and injection of 5-hydroxytryptamine, reduced the tumour blood flow and the anti-5HT agent cyproheptadine reversed the effect of 5-HT.

Most of the recent evidence is against the popular concept that there is considerable blood flow through tumours GULLINO & GRANTHAM (1961b) by direct measurement of the venous outflow of tumours transplanted into ovary or kidney found an average blood supply of 0 14 ± 0 01 ml per hour per mg $N_2$ compared with 7 18 ± 0 12 for normal ovaries and 6 9 ± 0 27 for control kidneys. The oxygen tension in tumours is usually low and responds rather slowly to inhalation of oxygen (URBACH & NOEL 1958 CATER & SILVER 1960 CATER, SCHOENIGER & WATKINSON 1962 1963) The oxygen tension in tumours is much reduced by lowering the blood pressure (CATER, GRIGSON & WATKINSON 1962) KOLSTAD (1963) has correlated low tissue oxygen tension and slow response to oxygen inhalation in carcinoma of the cervix with wide intercapillary distance and tortuous vessels detected by colpomicroscopy The dye injection techniques of GOLDACRE & SYLVÉN (1962) and OWEN (1960) show absence of blood flow in the central portions of many tumours CATALAND COHEN & SAPIRSTEIN (1962) using a radioisotope technique confirmed GULLINO & GRANTHAM's findings of a low blood flow through tumours. On histologic examination many tumours show areas of necrosis (THOMLINSON & GRAY 1955) and this is in favour of inadequate vascularisation and possibly a low blood flow

In favour of a large blood flow through tumours may be cited the increased oxygen content of venous blood draining neoplasms (BIERMAN KELLY & SINGER 1952) although this may be explained by the presence of arteriovenous shunts. The vigorous capillary bleeding which occurs when a tumour is incised during operation is in favour of free blood supply but it is noteworthy that granulation tissue also shows this troublesome type of bleeding which may be explained by a failure of the immature and imperfectly formed vessels to react to trauma by vasospasm.

These special features of tumour blood flow may play an important part in the tumour/host relationship Tumours are often thought to grow very rapidly but even those which grow fastest grow in fact more slowly than the human foetus and in many tumours the rate of growth is very slow by comparison with liver regeneration or epithelial cell replacement in gut and skin A slow growth rate in spite of active cell division can be explained by a high death rate in tumour cells Some may die from nuclear abnormalities others because of an inadequate blood supply In this respect the presence of many dilated capillaries does not necessarily mean a rapid blood flow for the blood in a dilated capillary may be flowing very slowly or not at all It is well known that many malignant tumours show abundant evidence of necrosis but the important part played by toxic absorption from this dead material in the production of cancer cachexia does not seem to be sufficiently appreciated

Toxic absorption from dead cells also sets a limit to the rate at which it is safe to destroy a large tumour In fact, one of the best features of radiation is that it kills cells slowly and an important feature of surgical excision of tumours is that it removes the dead tissue from the body

The tumour circulation is a weak link in the organisation of the tumour and it may be possible to exploit this weakness in cancer therapy The bacterial polysaccharide, purified by SHEAR and his associates, would appear to work by damaging the vessels and causing haemorrhages in tumour (It is noteworthy that it is much more toxic to the tumour bearing than to the normal animal (SHEAR 1941 SHEAR & PERRAULT 1944) Unfortunately the peripheral portions of the tumours often survived and the tumours regrew The special absorption of certain drugs in tumours may be due to slow blood flow through tumours or may be increased by this. The action of heat may be greater on tumours because of poor blood flow (CATER, SILVER & WATKINSON 1964) This action of heat is increased by 5-HT (CRILE 1963) In general agents which cause low blood pressure or damage endothelium, or increase the inflammatory reaction, will tend to retard the blood flow and tend to cause haemorrhages or thromboses and necrosis in tumours. Deliberate attempts to kill anoxic tumour cells by such methods have obvious dangers with large tumours, but with more knowledge of the physiologic aspects of tumour vascularity it might be possible to exploit these methods in radiotherapy The evidence presented in this paper that heat or 5-HT can reduce tumour blood flow and that the effect of the latter can be reversed by the anti 5-HT antihistamine agent cyproheptadine, may be useful in this respect.

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## ZUSAMMENFASSUNG

Abkühlungskurven von transplantierten *Rattentumoren und spontanen Mammakarzinomen* bei Mäusen, nach Erhitzung der Tumore mit 10 cm Kurzwellenbestrahlung wurden durch Komputationsanalyse matematisch beurteilt. Eine den experimentellen Ergebnissen gut entsprechende Formel wurde erreicht. Die Veränderungen der Temperatur Abhängigkeit der Abkühlungsgeschwindigkeit wurden als Veränderungen der Tumor Blutzirkulation aufgefasst. Erhitzung der Tumoren und Injektion von 5-Hydroxytryptamin verursachte *eine Reduktion der Blutzirkulation* der Tumoren, Cyproheptadin (das Anti-5-HT Agens) dagegen kehrte die Wirkung von 5-HT um.

## RÉSUMÉ

*Les courbes de refroidissement* de tumeurs transplantées sur des rats et de cancer du sein spontané de la souris, obtenues après échauffement des tumeurs par diathermie à microondes de 10 cm ont été analysées mathématiquement et par ordinateur On a établi une formule qui concorde exactement avec les résultats expérimentaux. Les modifications de la vitesse de refroidissement dépendant de la température ont été interprétées comme liées aux modifications du débit sanguin tumoral. L échauffement de la tumeur et l injection de 5-hydroxytryptamine réduisent *le débit* sanguin tumoral et le cyproheptadine, agent anti-5-HT inverse l effet du 5-HT

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FROM THE DEPARTMENT OF RADIOLOGY (DIRECTOR PROF MAGNUS STRANDQVIST)
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SAHLGRENSKA SJUKHUSET GOTHENBURG, SWEDEN

# TREATMENT OF RADIATION DERMATITIS WITH FLUOCINOLONE ACETONIDE

by

A. Björnberg, L. Hellgren and S Olsson

The reaction resulting from radiation in human skin can be undesirable and attempts in the past have been made to modify it by cortisone preparations administered either topically or generally The results so far have proved equivocal, however

Kalz & Scott (1956) investigated the action of topical applications of 1 % hydrocortisone, 0.2 % fluoro-hydrocortisone and 5 % corticotropine in grenz ray erythema (950 R, 1 140 R and 1 360 R, FSD 10 cm, HVT 0 022 mm Al, field 2 cm diameter) These topical steroids were capable of either completely suppressing partially inhibiting or delaying the erythema at different dose ranges. Sweet (1962) treated eleven patients who had accidentally received very large skin doses of roentgen rays instead of grenz rays. Therapy comprised local application of hydrocortisone ointment with prednisolone orally He found that the treatment did nothing to save the damaged epidermis but felt that it did affect to some degree the dermal reaction during the third and fourth weeks, and perhaps even longer

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Fig. 1 Roentgen-treated fields in post-operative mammary carcinoma. The supraclavicular and parasternal fields were chosen for the comparative topical treatment of radiation reaction.

Poschl (1957) irradiated guinea pigs and albino rats with single dosages of 2 000 to 2 500 R (FSD 1.5 cm) and subsequently treated them with cortisone, given either locally (ointment) or by intramuscular injection. This author was unable to demonstrate any suppression of the radiation reaction by cortisone. However he noted a somewhat stronger reaction, characterized by infiltration and ulceration at the radiation site in those animals which had received *local application* of cortisone

The controversial results obtained from various investigations may be due to the fact that the relationship differed between the anti-inflammatory effect of the steroids and the intensity of the radiation reaction induced.

Fluocinolone acetonide (Synalar[1] a product of the Syntex Corporation, is manufactured by ICI Ltd it was supplied by AB Meda, Gothenburg) provides us with a very potent steroid for local treatment The anti-inflammatory effect of this drug in investigations on adrenalectomized rats by the cotton pellet implant technique has been found to be 35 times greater than that of cortisone and 7 times greater than that of triamcinolone The 16—17 acetonide produces an anti-inflammatory effect that is about 100 times greater than that of hydrocortisone (Mills et coll. 1960) Fluocinolone acetonide has been extremely effective in the treatment of eczema (Björnberg & Hellgren 1962) as well as in cases of psoriasis, discoid lupus erythematosus, and palmoplantar pustuloses (Björnberg & Hellgren 1962, 1963) One of the present authors

MARSHALL (1953) irradiated mice with a single dose of 3 500 to 4 000 R (60 kV 4 mA FSD 3 cm, HVT 2 8 mm Al) and subsequently treated one series of animals with cortisone parenterally from the day before until three to six days following radiations and a second series with cortisone from the seventh day after radiation until sixteen days after lesions had developed. Both the cortisone treated groups were compared with two control series of untreated animals. In the first cortisone treated group lesions appeared after 17 days, and in the control group after 15 days In the second cortisone-treated group lesions appeared after 21 days and in the control group after 15 days The severity of the reaction was reduced by treatment with cortisone

BRUCE & BARCLAY (1960) investigated the effect on rabbits ears of 2 5 % cortisone in an ointment base, on local reactions after a single dose of 5 000 R (250 kV HVT 0 25 mm Cu FSD 45 cm) The treatment with cortisone commenced two days prior to irradiation and continued for 35 days. Untreated ears exhibited severe radiation reaction after 15 to 30 days, whereas little erythema was present on the cortisone treated ears after 30 days although there was complete epilation and fine scaling Shortly after the cortisone was discontinued marked desquamation and exudation appeared and was followed by ulceration and infection

HOUGHTON WALTER & JONES (1954) irradiated guinea pigs with 6 000 R divided into two equal doses with a 48 hour interval between them (50 kV 2 mA HVT 1 7 mm Al FSD 3 cm 2 6 cm circular field) after which the animals were given cortisone parenterally They exhibited no local ulceration, whereas the untreated animals developed persistent ulceration and cicatrization The early erythema was reduced during cortisone treatment and epilation was also delayed

MALLET WALTER & HOUGHTON later (1961) reported that the skin damage arising in guinea pigs that had received roentgen irradiation in single doses of 5 000 R could be divided into two phases an early phase occurring after 3 to 6 weeks with desquamation and superficial (epidermal) moist ulcers, and a later phase commencing after about 6 weeks with necrosis of the dermis and deeper tissues Cortisone given parenterally for 42 days had no preventive effect on the first phase but postponed the latter reaction

As opposed to the above mentioned authors who found that cortisone reduced the radiation reaction others have been unable to establish the existence of such an effect MORALES (1953) for example reported that the intensity of the human skin reaction after 5 days (single doses of 200 R 300 R 350 R 120 kV 5 mA FSD 20 4 cm HVT = 0 8 mm Al 5 cm circular field) was not reduced by parenteral therapy with ACTH and cortisone The cortisone treated patients were compared with controls who had not received cortisone



Fig 2 Radiation reaction in the supraclavicular (fluocinolone acetonide treated) and in the parasternal (placebo treated) fields after 3 weeks

(L. H.) previously observed a good effect when fluocinolone acetonide was administered therapeutically and prophylactically in radiation dermatitis.

*Material and Methods.* The investigation covered 26 patients, 24 women and 2 men, all of whom were receiving roentgen therapy for malignant tumours. Twenty patients had mammary carcinoma, one carcinoma of the nasal cavity, one carcinoma of the urinary bladder with skin metastases, three carcinomas of the cervix of the uterus, and one patient had carcinoma of the ovary. Most of the patients received a total dosage of 3 000 R per field (2 400—3 600 R) with a daily skin dosage of 300 R (including backscatter), FSD 40 cm, HVT 0.8—1 mm Cu, dosage rate 85—100 R/min.

Patients being treated for abdominal tumours received symmetric irradiation to the left and right sides; the irradiated fields are comparable. In the treatment of mammary carcinoma four fields were irradiated (Fig. 1). The supraclavicular and the parasternal fields were used in the comparative study, the size of these fields varying between 50 cm² and 225 cm². As regards the skin reaction of ionizing radiation these fields may not be quite comparable. The changing contour of the supraclavicular field may give rise to somewhat different absorption and reaction, and the bone tissue beneath the parasternal field may cause more secondary radiation. The fluocinolone acetonide ointment was applied alternatively to the two fields in different patients in order to compensate for these factors. Of the 20 patients who were treated for mammary carcinoma, 13 received fluocinolone acetonide on the supraclavicular field and the ointment base on the parasternal field.

The application of ointment to the irradiated sites was commenced at the same time as the initial roentgen treatment and continued throughout the entire observation period. During the study 0.025 % fluocinolone acetonide in a bland base (propylene glycol 5.0 g, hydrogenated lanoline 10 g, paraffin ad 100 g) was used, the base alone being administered as placebo. The patients on discharge from hospital were given two unmarked tubes, containing the active substance and placebo respectively for continued treatment at home. The ointments were to be applied 2 to 3 times daily to the respective fields. The patients were re-examined after about 3 weeks and again after about 6 weeks (23 patients) and the degree of reaction assessed. This was graded between 0 and 5 by the physician, 1 indicating erythema, 3 dry dermatitis and 5 signifying exudative dermatitis, 2 and 4 were intermediate.

## Statistical analysis

A parametric test (student's test) and a non parametric test (the "sign test") were used in the statistical analysis of the results. The level of significance is 0.05.

*Radiation reaction after 3 weeks*

*Student's test.* The mean value of the numerical expression for the radiation reactions in 26 patients was $\bar{x} = 1.65$ for the fluocinolone acetonide treated regions, and $\bar{x} = 2.77$ for the placebo treated regions. The variances were $s = 0.48$ and $s = 1.06$, $F = 2.2$. The difference between the mean values was significant at the 95 % level.

*Sign test.* The patients in whom fluocinolone acetonide was superior to the placebo were indicated with a plus sign and those in whom the placebo was superior to fluocinolone acetonide were marked with a subtraction sign. The patients showing no difference were marked 0. The distribution 18 + 3 — and 5 zeros was obtained the difference was significant.

After 3 weeks of treatment the fluocinolone acetonide treated fields thus exhibited less severe radiation reaction than the placebo treated fields.

*Radiation reaction after 6 weeks*

*Student's test* The mean value of the numerical expressions for the radiation reaction of the 23 patients was $\bar{x}_1 = 1.78$ for the fluocinolone acetonide treated regions, and $\bar{x} = 2.04$ for the placebo treated regions. The variances were $s = 1.00$ and $s = 0.96$ $F = 1.0$ the difference was not significant.

Sign test. The sign distribution was 10 + 5 — and 8 zeros and the difference was not significant.

After 6 weeks of treatment there was no longer any statistically significant difference in the reactions of the fluocinolone acetonide and the placebo fields. This may be explained by the fact that the radiation reaction naturally subsides spontaneously

Four patients exhibited the following phenomenon in the fluocinolone acetonide treated regions, during the fourth week. After an initial good effect on the radiation reaction, a rapid deterioration set in in these regions despite unchanged local treatment. The deterioration was characterized by a marked radiation reaction, which was more severe than any occurring in the corresponding placebo treated region throughout the entire observation period.

## SUMMARY

A double blind comparison was made of the topical treatment of radiation reaction with fluocinolone acetonide ointment and the ointment base alone in 26 patients receiving radiotherapy for malignant tumours. After three weeks the reaction was significantly less severe in the regions treated with the former: after six weeks the difference was no longer obvious, possibly due to spontaneous healing.

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# TUMOUR DOSE CONCEPT

by

L. SUNDBOM and P E. ÅSARD

It is recognized that with therapeutic irradiation the dose within the tumour volume is often not quite homogeneous even after careful dose planning. It is desirable, for facilitating comparisons to be made between different irradiation alternatives, as regards dose levels and radiation techniques for the individual patient and for different patients and patient groups, that the dose within the tumour volume can be represented by one figure. A generally accepted definition of the term tumour dose is therefore desirable.

ELLIS & OLIVER (1961) have discussed some alternative definitions of the tumour dose

1. *Median dose* the average of the maximum and minimum values in the tumour volume
2. *Average dose* the average value of the dose in the tumour volume.
3. *Modal dose* the dose most frequently occurring in the tumour volume

At a meeting held at the Royal College of Surgeons in England, the Faculty of Radiologists recommended the use of the modal dose as the definition of tumour dose for 4 to 8 MV-linear accelerators. Its application to cobalt 60

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## ZUSAMMENFASSUNG

Es wurde gezeigt, dass die Wirkung einer 0,025 % Fluocinolon-acetonid-Salbe nach 3 Wochen in der Behandlung von Strahlenreaktionen derjenigen der einfachen Salbenbasis überlegen ist. Die Untersuchung wurde als ein doppelter Blindversuch bei 26 Patienten durchgeführt. Die Strahlentherapie wurde für maligne Tumoren gegeben. Nach 6 Wochen war kein Unterschied zu verzeichnen, möglicherweise durch Spontanheilung.

## RÉSUMÉ

Chez 26 malades *traités par radiothérapie pour tumeur maligne, les auteurs ont fait une* comparaison au double insu du traitement local de la radiodermite par une pommade à l'acétonide de fluocinolone et par le seul excipient de la pommade. Au bout de trois semaines, les réactions étaient nettement moins graves dans les régions traitées par la fluocinolone; au bout de six semaines, la différence n'était plus évidente, probablement en raison de la guérison spontanée.

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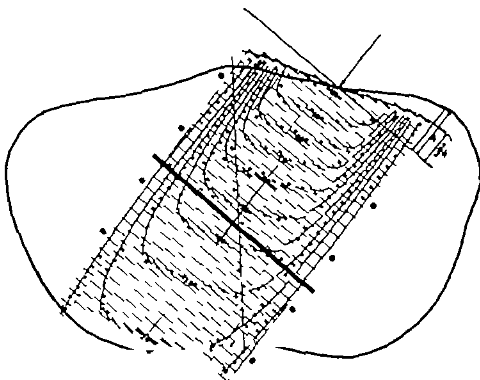


Fig. 2. Calculation of average dose. Correction for oblique incidence with special isodose diagram.

The study now presented of two-dimensional dose distributions is therefore limited to a comparison between modal dose and average dose as regards both the practical methods of calculation and the reproducibility. The examples with cobalt 60 radiation refer to both fixed beam and moving beam therapy.

## Calculation of modal dose and average dose

A grid is mounted over the tumour area in the determination of the modal dose by the Spiers & Meredith's method, as seen in Fig. 1. The doses from the different beams are summed up at the points of intersection between the lines of the grid. A histogram is drawn with the number of points on the vertical axis and the percentage dose on the horizontal axis. The dose value found at the largest number of points is called the modal dose. The average dose may also be obtained with the use of this grid by adding the doses at all the points and dividing the sum by the number of points.

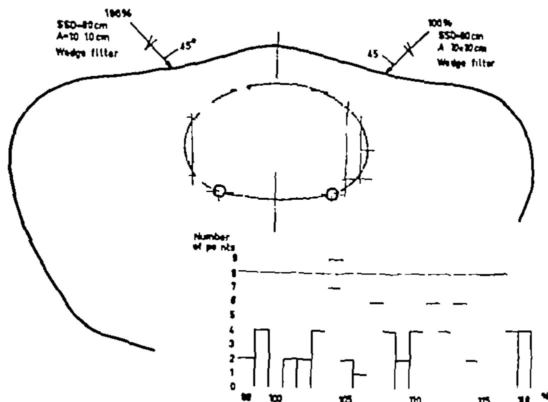



Fig 1 Illustration of calculation of modal dose. Broken line indicates tumour area. (The complete dose distribution is shown in fig 4 )

units was not explored in any detail but it was felt that it would be desirable and probably equally practicable to use it in fixed beam cobolt 60 therapy (SPIERS & MEREDITH 1962)

The suitability of these alternatives will now be discussed from the physical viewpoint

The definition of the tumour dose must in every particular case enable calculations to be made with sufficiently small margins of error The tumour dose should also be calculable in practice without an unreasonable amount of work. Furthermore the definition should be the same for all irradiation techniques and radiation qualities

Which of the above definitions, if any is most suitable from medical and biologic viewpoints can in the strictest sense be decided only if the tumour dose value obtained is related to the biologic effect. The median dose seems to be the least advisable, however as it is independent of how the energy absorbed per gram is distributed in the tumour volume The values of the median dose may for instance, be identical whether the larger part of the tumour receives a dose close to the maximum or near the minimum value

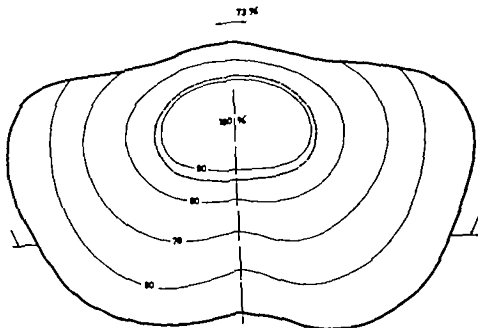



Fig 3. Dose distribution obtained with moving beam technique (isodose chart 082 in Hultberg et coll. 1959). Broken line indicates tumour area.

| | |
|---|---|
| Median dose | 94 ± 6 % |
| Modal dose | 88 $^{+12}_{-0}$ or 94 ± 6 % |
| A erage dose | 94 ± 6 % |

It appears from this that the average dose can be cal-ulated with fewer points than the modal dose.

The a erage dose has also been calculated by the planimeter method The value is 109 7 with only three areas, the area between 110 % and 100 % and the areas with larger and smaller doses, respectively than these.

Another way of proceeding is to project the tumour area into the standard isodose diagrams and calculate the average dose for each beam separately The number of areas between two isodoses, separated by 10 % of the peak dose will then be larger in this case 8 in each beam. The peak dose is the maximum value of the absorbed dose which occurs along the beam axis. The average dose was calculated as 109.8 % This method consequently gave values that were practically the same as those obtained with the grid method

Another example showing that the modal dose is dependent on the number of points, is seen in Fig 3 The irradiation is performed with the beam

Another possibility of calculating the average dose which may imply practical advantages, is illustrated in Fig 2 The grid is fixed to the isodose diagram instead of to the patient. The standard isodose diagram copied on thin perspex, is divided into strips, 1 cm in width This enables a correction for an oblique incidence to be made by displacing each of these strips at a fixed distance between the entrance surface of the diagram (which is perpendicular to the beam axis) and the body contour This displacement is two-thirds of the last mentioned distance as suggested by DUTREIX & DUTREIX (1962) The figures of the standard isodose diagram represent the average dose within an area of 1 $cm^2$ and are determined graphically The contribution to the average tumour dose from each beam is obtained by adding the dose values within the tumour area and then dividing the sum by the number of elements within the area The average dose for the entire planning is then obtained by adding up the average doses of all the beams The determination of the modal dose is more laborious in that the particular dose value from each beam must, as mentioned above, be noted and summed up at each point of the grid fixed to the tumour area.

A third method of calculating the average dose is by means of a planimeter The area between two isodoses is measured and multiplied by the mean value of the two doses this is done for the whole tumour area All the products are then added and the sum is divided by the tumour area. The dose intervals in this case are thus constant in the other two methods the areas are constant.

*Examples* Certain difficulties may arise in the determination of the modal dose as will be seen from the example in Fig 1 The modal dose is calculated to be 115 % or 116 % for these two beams with wedge filters if the two points of intersection marked with circles in the figure are ignored If on the other hand these points are assumed to be situated within the tumour area, the modal dose will be 104 % This shows that the modal dose may depend on the positioning of the grid The average dose is in both cases 110 % (109 7 % and 109 5% respectively) This is not surprising as the two points each representing an area of 1 cm cannot of course have any notable effect if the definition of the average dose is taken into account

The modal and average doses have for this example also been calculated with a more open grid one with a linear distance of 2 cm Every other line in the grid is left out with the same mounting as in Fig 1 This produces four different series of points of intersection The encircled points have not been taken into account i e the modal dose for the original grid is 115 % or 116 % The modal dose is in the different cases 115 % 116 % 104 % and 113 % the average dose being 108 9 % 109.5 % 109 5 % and 110 5 % respectively

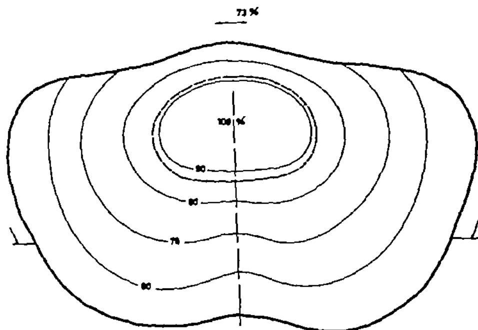



Fig 3 Dose distribution obtained with moving beam technique (isodose chart 082 in HULTBERG et coll 1959) Broken line indicates tumour area

| | | |
|---|---|---|
| Median dose | $94 \pm 6$ | |
| Modal dose | $88 {}^{+12}_{-0}$ | or $94 \pm 6$ |
| Average dose | $94 \pm 6$ | |

It appears from this that the average dose can be calculated with fewer points than the modal dose.

The average dose has also been calculated by the planimeter method. The value is 109 7 % with only three areas, the area between 110 % and 100 % and the areas with larger and smaller doses, respectively than these.

Another way of proceeding is to project the tumour area into the standard isodose diagrams and calculate the average dose for each beam separately The number of areas between two isodoses, separated by 10 % of the peak dose will then be larger in this case 8 in each beam The peak dose is the maximum value of the absorbed dose which occurs along the beam axis The average dose was calculated as 109 8 This method consequently gave values that were practically the same as those obtained with the grid method

Another example, showing that the modal dose is dependent on the number of points, is seen in Fig 5 The irradiation is performed with the beam

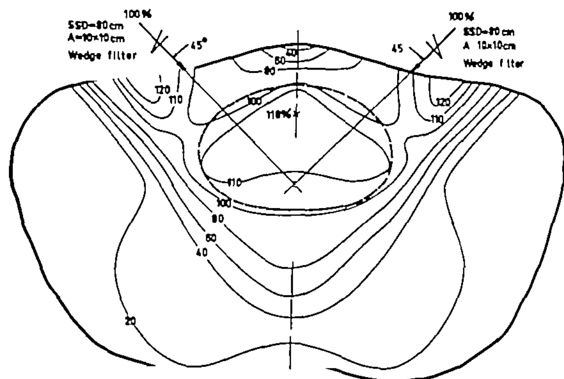



Fig 4 Dose distribution resulting from two beams with wedge filter Broken line indicates tumour area

| | | |
|---|---|---|
| Median dose | 108 + 10 | |
| Modal dose | 101 $^{+14}_{-6}$ | or 116 $^{+2}_{-18}$ |
| Average dose | 110 $^{+8}_{-12}$ | |

oscillating 180 The modal dose is determined at 94 % using a grid with a linear distance of 1 cm if a sufficiently dense grid is used the modal dose will be equal to the minimum dose (88 %) This obtains at all dose distributions where the dose falls approximately linearly from the centre towards the periphery as at the same time the area and consequently the number of points increases with the square of the distance from the centre If the dose decreases with the square of this distance all values from the maximum to the minimum have the same frequency This means that the modal dose can not be determined at a definite value

The average dose has also been calculated for this example The value of 93.5 % was obtained when a grid with a linear distance of 1 cm was used and the values were 93 7 % 93 6 % and 93 6 % respectively when the average dose was calculated by means of the planimeter method with dose intervals of 2 % 5 % and 10 %

*Comparison of treatment plannings* Two dose plannings for the same patient were used in the above to exemplify calculations in accordance with two different definitions of tumour dose. The dose distribution for the moving beam alternative is shown in Fig 3 and the one with two wedge filter beams in Fig 4 A suitable standardization has to be made for a comparison of these two treatment alternatives as regards the dose distribution within and outside the tumour area. The isodoses as represented in the figures are functions of the peak doses of the standard isodose diagrams. The most suitable principle should then be to standardize the treatment plannings to the tumour dose If these were standardized to the average dose, the maximum doses (in %) in the two treatment alternatives would be approximately identical, whereas the minimum doses would be lower in the wedge-filter beam alternative. This comparison shows that the latter alternative gives a lower minimum dose at the same total dose absorbed within the tumour

## Discussion

It would be most valuable if one definition of the term tumour dose could be accepted and used at all radiotherapy clinics. The definition must be such that the calculations in every particular case are reproducible within desired limits, and may be performed without an unreasonable amount of work. The average dose would appear to be preferable to the modal dose. The examples of irradiations chosen to illustrate this may seem unfavourable, as the maximum dose variation is $\pm$ 10 %. The definition must, however also be valid for such types of irradiation, since they are used in practice, for instance when a certain dose value must not be exceeded in a radiosensitive organ. When the dose variation within the tumour area is small, the difference between the modal and average dose is of course very small but the practical advantages in the calculation of the average dose still remain. If the calculation of the tumour dose is to be extended to the whole tumour volume, it is of particular advantage if the number of points of calculation are not too high. Apart from the average dose, it would appear to be most important that the maximum and minimum dose values within the tumour area are stated at the dose planning

## SUMMARY

It would be an advantage if the term 'tumour dose' could be uniformly defined in order that comparisons of different patients and patient groups as regards dose levels and radiation techniques could be facilitated. It is suggested that the 'average dose' may be the best one to use

## ZUSAMMENFASSUNG

Es erscheint wünschenswert dass der Ausdruck Tumordosis einheitlich definiert wird, damit Vergleiche zwischen verschiedenen Patienten und Patientengruppen bezüglich Dosenabgabe und Bestrahlungstechnik leichter vorgenommen werden können Es wird angeregt, dass der Ausdruck „Durchschnittsdosis am brauchbarsten ist

## RÉSUMÉ

Il est souhaitable que le terme « tumour dose » reçoive une définition uniforme pour faciliter la comparaison entre divers malades et groupes de malades en ce qui concerne les doses et les techniques d irradiation. Les auteurs pensent que le terme « average dose » (dose moyenne) est le meilleur

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FROM THE GYNECOLOGIC SECTION (DIRECTOR ASSISTANT PROF OLLE KJELLGREN)
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# FURTHER DEVELOPMENT OF THE HEYMAN RADIUM PACKING METHOD

by

Olle Kjellgren and Lars Jonsson

The treatment of cancer of the body of the uterus has long been a matter of controversy Some are in favour of primary surgery with or without post operative radiotherapy while others prefer radiotherapy with or without postradiation surgery Today most investigators agree that some of the carcinomas of the corpus uteri, e. g the highly differentiated adenocarcinomas in an early stage can be operated upon primarily These cases need however postoperative radium treatment of the vagina to lower the risk of postoperative vaginal metastases. Advanced cancers of the corpus, although highly differentiated, should be treated with preoperative radiation to achieve a good result. Low-differentiated tumours of the corpus must, however without exception be treated primarily with radiation and later in operable cases, with total extirpation of the uterus, tubes and ovaries in so doing one may expect the best results possible Primary surgery in low-differentiated carcinomas of the corpus, even though clinically limited to the uterine cavity is connected with a poor prognosis (Kottmeier 1959)

Submitted for publication 27 April 1964

Table 1

*Irradiators used at Radiumhemmet*

| Irradiator No. | Radium tubes | | | Additional filters | |
|---|---|---|---|---|---|
| | Radium content | Size | Filtration | Size | Filtration |
| 0 0 | 10 mg | 14 × 2.3 mm | 0.2 Au + 0.3 Pt = 0.8 mm Pb | 18 × 5.1 mm | 2 mm Pb |
| 0.5 | 10 mg | » | » | 18 × 6.3 mm | » |
| 1 | 8 mg | 20 × 2.8 mm | 0.35 Au + 0.3 Pt = 1 mm Pb | 25 × 7.8 mm | 2 mm Pb |
| 2 | 8 mg | » | » | 26 × 9.8 mm | » |
| 3 | 8 mg | » | » | 27 × 11.8 mm | » |
| 4 | 8 mg | | » | 29 × 13.8 mm | |

Some institutions in which gynecologic cancer therapy is centralized prefer to treat cases of carcinoma of the body of the uterus primarily with radiation, supplemented when suitable with surgery. This mode of treatment has certain advantages, e. g. the cases are centralized for uniform evaluation and diagnosis in a hospital where expert treatment can be given. It carries, however, the disadvantage that some of the early and highly differentiated adenocarcinomas of the corpus which could instead have been operated upon primarily and the patient later sent for postoperative vaginal radium therapy, will not receive this treatment.

## The Heyman radium packing method

The primary radium treatment of cases of cancer of the corpus has varied. The radium packing method developed by Heyman, in which a suitable number of irradiators are used to "balloon out" the uterine cavity, appears, however, to have been the most successful. The method has been thoroughly described by Heyman, Reuterwall & Benner (1941) and Heyman & Benner (1946). They recommended a dose of about 3 000 R at a distance of 1.5 cm from the nearest irradiator, regardless of the number of irradiators used. This corresponds approximately to the serosal surface of the uterine corpus. The dose in the bladder and the rectum is measured and a dose to the anterior wall of the rectum of 4 000 to 5 000 R, part of which comes from the vaginal radium, should not be exceeded. The radiation dose is given in two or three applications.

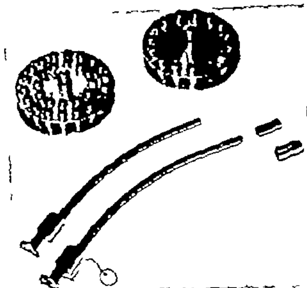


Fig. 1. The permanently closed irradiator, additional filters and applicators.

The original equipment of HEYMAN & BENNER for packing the uterus with a number of irradiators of uniform size and shape was based on the use of radium tubes having an external length of 20 mm and an outside diameter of 2.8 mm. The wall thickness was equivalent to 1 mm of lead (0.35 mm Au + 0.30 mm Pt) and each radium tube contained 8 mg of radium element. The radium tube was placed in a tube holder with a screw plug and to this an additional filter of suitable size was attached. A string with a badge was fixed to the irradiator which was applied to the uterine cavity by specially constructed applicators. The original additional filters had diameters of 7.8, 9.8, 11.8 and 13.8 mm for filter numbers 1, 2, 3 and 4, respectively. Later, in 1946, HEYMAN & BENNER introduced two smaller sizes of additional filters with a diameter of 5.1 and 6.3 mm; these, called No. 0.0 and No. 0.5 respectively, were made of gold and carried 10 mg of radium. The original four sizes of the filters have an inner wall of lead and an outer wall of stainless steel, both of equal thickness, in order to keep the radiation transmission constant. There will therefore be an air space between the inner and outer walls, the size of which will depend on the filter sizes. Details of the filters, the radium tubes and the filtration are collected in Table 1.

This equipment for packing the uterine cavity by multiple irradiators has many advantages. It possesses, however, certain hazards. The personnel hand

Table 2

*Irradiators used by the authors*

Permanently closed irradiator (No 0)

| Length | Diameters Inner Outer | Wall thickness | Radium tube | Total filtration | Dose rat at 1.5 cm |
|---|---|---|---|---|---|
| 20 mm | 3 mm 6 mm | 1 5 mm steel | Radium content 10 mg<br>External length 17 mm<br>Active length 10 mm<br>Di meter 2 9 mm<br>Filtration 2 mm Pb | 2 4 mm Pb | 32.2 rad/h = 100 |

Additional filters

| No. | Length | Diameters Inner Outer | Wall thickness | | |
|---|---|---|---|---|---|
| 1 | 22.5 mm | 6.1 mm 8 mm | 1 mm steel | 2 6 mm Pb | 30 8 rad/h = 96 |
| 2 | 23.5 mm | 6 1 mm 10 mm | 2 mm steel | 2 7 mm Pb | 29.9 rad/h = 93 |

ling the equipment are exposed to gammaradiation a danger that is likely to arise when the radium tubes are transferred from the storage to the instrumental equipment and put into the tube holders and especially when the additional filters are screwed on the screw plugs with the radium tubes. The handling of the equipment with the irradiators ready for application also entails some risk Special shielding arrangements had therefore to be made (WALSTAM RAGNHULT et coll. 1962)

## Present authors instrumental equipment

The aim of the further development of the Heyman radium packing method has been to make the handling of the irradiators and additional filters as practical as possible and to reduce the radiation hazards Permanently closed irradiators of small size called No 0 and additional filters so constructed that they could be pushed on this irradiator immediately before the application in the uterus have therefore been used A special tool to remove the additional filter from the irradiator has also been constructed

Table 3

*Treatment times in hours to deliver 1000 rad at 1.5 cm depth with different numbers and sizes of irradiators*

| Numbers of irradiators | Irradiator No. 0 | 1 | II |
|---|---|---|---|
| 6 | 15 1/2 | 19 | 21 1/2 |
| 7 | 14 3/4 | 18 | 20 |
| 8 | 14 | 17 | 18 3/4 |
| 9 | 13 | 16 1/4 | 17 1/2 |
| 10 | 12 1/4 | 15 1/4 | 16 1/2 |
| 11 | 11 1/2 | 14 1/2 | 15 1/2 |
| 12 | 10 3/4 | 13 3/4 | 14 3/4 |
| 13 | 10 1/4 | 13 1/4 | 14 |
| 14 | 9 3/4 | 12 3/4 | 13 1/2 |
| 15 | 9 1/4 | 12 1/4 | 13 |

*The permanently closed irradiator for intrauterine packing* Most cases of cancer of the corpus can be packed sufficiently by using 10 to 15 irradiators No. 0 loaded with a radium tube of the standard type T5 manufactured by the Radiochemical Centre, Amersham, Buckinghamshire, England. The tube contains 10 mg of radium and has a length of 17 mm (active length 10 mm) a diameter of 2.9 mm, and a sheath of 10 % IrPt of 1 mm wall thickness. The container is of stainless steel, with an outer diameter of 6 mm and a length of 20 mm, and is permanently closed. A small eyelet at one end is for the attachment of a thin steel wire with a numbered badge (Fig 1)

The total filtration of this irradiator is 1 mm IrPt + 1.5 mm steel, which is equivalent to about 2.4 mm of lead or 1 15 mm of platinum. When the width of the uterine cavity demands larger irradiators, additional filters, sizes 1 or 2, are attached to the irradiator

*The additional filters* A high primary filtration of the radium tube (2 mm of lead) has some advantages. The radiation quality is very little influenced when filters of steel are added to the radium tube. The decrease in output is even smaller with increasing filtration when the primary filtration is high. The change in radiation quality by the addition of about 2 mm steel to the irradiator may be neglected. The change in output must however be taken into account the measurements obtained are given in Table 2.

The additional filters are made of stainless steel. A groove at a distance from the bottom somewhat greater than the length of the irradiator is cut in the inner wall of the open end of each filter A spring of ellipse shape is placed in

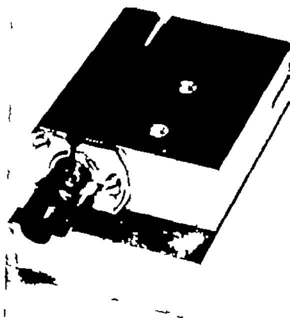


Fig 2 Removing instrument insert.



Fig 3 Irradiator handling tool.

the groove. When the irradiator No 0 is attached to the additional filter the spring is expanded by the irradiator and then locked behind it. Two additional filters, sizes Nos 1 and 2 are used The inner diameter of both filters is 6 1 mm, and the outer diameter is 8 and 10 mm, respectively The additional wall filtration will be 1 mm and 2 mm respectively which will give a total filtration of about 2 6 mm and 2 7 mm of lead for irradiators Nos 1 and 2, respec

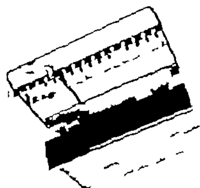


Fig. 4. Frame with applicator and insert.

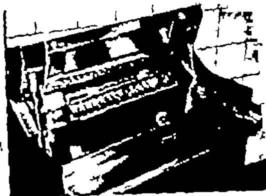


Fig. 5. The radium cart loaded with irradiators ready for use.

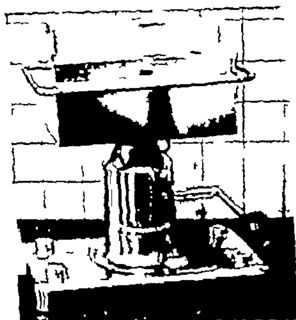


Fig. 6. The radium cart.

tively The equivalent platinum filtration is 1.2 mm and 1.25 mm. The data are collected in Table 2.

The intrauterine radium packing treatment used in the department is based on three treatments at two-week intervals. A dose of approximately 1 000 rad is administered to a point 1.5 cm from the nearest irradiator in the corpus, i. e. a total dose of 3 000 rad in four weeks. The treatment times with

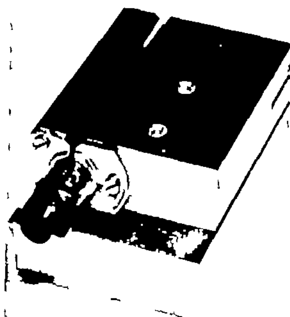


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## ZUSAMMENFASSUNG

Eine weitere Entwicklung der Heyman Radium Packung mit höherer Primärfiltrierung der Radiumröhre wird mitgeteilt. Die Radiumröhre ist dauernd in einer rostfreien Stahlröhre eingeschlossen um das dauernde neue Laden zu vermeiden. Neue Methoden zur leichten Auswechselung des Filters, neue Greifzangen, und ein neuer Radiumtransportwagen, wurden ebenfalls eingeführt.

## RÉSUMÉ

Description d'un nouveau perfectionnement de la méthode de packing de Heyman, basé sur une forte filtration primaire du tube de radium. Le tube de radium est enfermé de façon permanente dans un étui d'acier inoxydable pour éviter d'avoir à charger l'étui. Cette technique se caractérise encore par un moyen permettant d'ajouter ou d'enlever rapidement des filtres additionnels, ainsi que par des instruments de manipulation du radium spéciaux et par un chariot à radium.

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different numbers of irradiators of different sizes calculated from the measurements performed by BENNER (see HEYMAN & BENNER 1946) with due consideration of the change in output and filtration are collected in Table 3

*Equipment for removing the additional filters* The irradiators after being used are put into a shielded container in the ward First they are immersed in a saline solution to avoid incrustations and then they are washed in an ultrasonic cleaning tank before being placed in the radium cart. This procedure is the same for all the types of radium irradiators used by the department.

A semi automatic instrument for removing the additional filters is shown in Fig 2 This is shaped as an insert to the universal irradiator handling tool that forms part of the radium storage unit The tool, which has been developed in the department is supplied with a radiation shield to reduce radiation hazard to the hands (Fig 3) The mechanism of the removing instrument consists of two cylindrical plungers placed concentrically both are spring loaded and have a common slit for the steel wire. It functions as follows. The irradiator is placed on the semi-cylindrical irradiator holder in front of the plungers. When the irradiator is forced towards the plungers by a manual pull on the steel wire the inner plunger acts on the small spring in the additional filter which is expanded to release the irradiator The outer plunger works on the additional filter and pushes it off The filter is then easily removed with forceps This forms a rapid and handy procedure which is much quicker than unscrewing the additional filters as was necessary in the Heyman Benner technique.

*The radium cart* A special radium cart has been developed for storing and transporting the permanently closed irradiators the radiation shielding is sufficient for 15 irradiators The cart contains a stainless steel insert surrounded by a lead shield one part of this shield forms a cover The insert is easy to remove for sterilization. The lead shield is covered by a stainless steel envelope mounted on the base of a surgical operation table the hydraulic system of which is modified to open or close the heavy cover (See Figs 5 and 6)

The irradiators No 0 fitted to their applicators, are arranged (Fig 4) in a straight line in numerical order in the frame for convenience of handling at the application The frame is sterilized and placed in the insert container

## SUMMARY

A further development of the Heyman radium packing method, based on a high primary filtration of the radium tube is described The radium tube is permanently closed in a container of stainless steel to avoid the loading procedure. A rapid means of attaching and removing additional filters, special handling tools and a radium cart, are special features of the technique.

the hemispheric end face of a silver wire this face was made the anode of an electrolytic cell. Deposition on other parts of the wire was prevented by a thin layer of paraffin wax. A tall glass beaker of 5 ml volume was used as the electrolysis vessel this was tightly closed with a rubber stopper which also served as holder for the electrodes placed near the wall.

Carrier free iodide (20 mCi Na $^{125}$I) was obtained from Oak Ridge National Laboratory U.S.A., the active material being delivered as a 2 ml aqueous solution of sodium hydrogen sulphite. Inactive iodide carrier was added to a concentration of 0 0001 M This solution without purification was then used as electrolyte.

The solution was efficiently stirred during the deposition. The current strength at the beginning of the electrolysis, 0.20 μA (50 μA/cm ) was estimated to be near its limiting value with respect to deposition of iodide under the conditions used. During the deposition, which was continued for eighty hours, the current was decreased stepwise to suppress competing anodic processes (cf. LINGANE 1958)

After electrolysis the active tip of the wire was covered with a plastic material to prevent mechanical loss of activity

It was desirable, in view of the expense involved, to deposit the radio-iodide quantitatively but, because of the presence of hydroxide and sulphite ions in the electrolyte, silver oxide and possibly also silver sulphite, were formed in addition to the silver halide However after three days electrolysis 60 % of the radio-iodide was found to have been deposited.

It is obvious that an alkaline solution is not ideal as an electrolyte Even a neutral solution should be avoided (LINGANE & SMALL 1949) since, because hydroxide is generated at the cathode, it becomes alkaline during electrolysis. The electrolysis should be carried out in a buffered acid medium and at accurately controlled anode potential to prevent co-deposition of oxide. Iodide ions in an acid medium tend, however to be oxidised to free iodine by dissolved air and this iodine may escape to the atmosphere. An alkaline solution has been used in the experiments to eliminate this risk as far as possible.

Later on, a source of 250 mCi strength was prepared with 500 mCi carrier free Na $^{125}$I solution supplied by the Nuclear Science and Engineering Corporation, Pittsburg, U.S.A. This roentgen source was prepared by electrodeposition from 2 ml of a solution containing 0.23 micro-moles of $^{125}$I (500 mCi) to which had been added an equivalent amount of inactive iodide. Calculated from these known concentrations the apparent current efficiency with respect to the formation of AgI was about 50 % at the beginning of the electrolysis. The evident current losses might be due to the presence of inactive iodide in the carrier free solution obtained from the supplier The observed value for

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# IODINE 125 AS A RADIATION SOURCE WITH SPECIAL EMPHASIS ON ITS APPLICATIONS IN MEDICAL RADIOLOGY

## II AgI and CuI as point roentgen sources

by

P BERONIUS, S FORBERG C.-O HENRIKSSON and R SÖREMARK

Some aspects of the use of $^{125}$I as a source of roentgen radiation were indicated in part I of this paper The purpose of the present article is to discuss the concentration of this nuclide to a point source by electrolytic deposition on the end of a thin silver wire and to describe the portable roentgen unit developed (cf BERONIUS et coll 1962) The results of attempts to use copper in place of silver as backing material for the deposit are also reported As was shown in part I it is more advantageous to deposit $^{125}$I on copper because of the smaller self absorption losses of roentgen rays in copper iodide than in the corresponding silver halide

*Preparation of AgI roentgen sources* A $^{125}$I roentgen source, 0 5 mm in diameter and of 12 mCi strength, was prepared by electrolytic deposition of iodide ions on

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the hemispheric end face of a silver wire this face was made the anode of an electrolytic cell. Deposition on other parts of the wire was prevented by a thin layer of paraffin wax. A tall glass beaker of 5 ml volume was used as the electrolysis vessel this was tightly closed with a rubber stopper which also served as holder for the electrodes placed near the wall.

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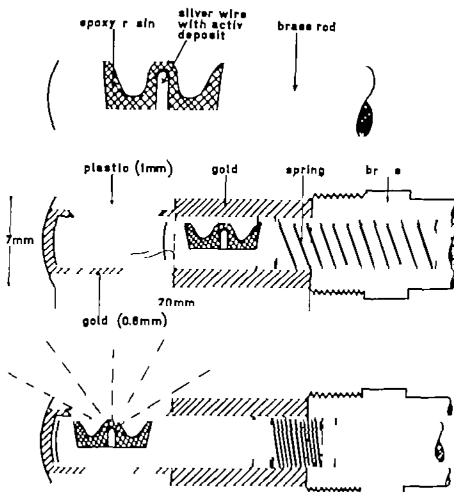



Fig 1 Sections of the roentgen unit. Middle portion non-exposure position. Lowest portion exposure position.

the current efficiency indicates that the amount of carrier iodide could be at the most twice the quantity of radio-iodide Actually the deviation of the current efficiency from 100 % can mainly if not completely be attributed to competing anodic processes, e g the formation of silver oxide. It follows therefore that the specific activity of the $^{131}$I as supplied was considerably larger than 30 % as a matter of fact the specific activity might have been 100 % This source, which was of sufficient strength to be employed for clinical purposes, was coated with a thick layer of an air hardening epoxy resin (Aral dite AZ 102 marketed by CIBA) and enclosed in a device of the type described in the following section This resin was selected because of its con venient application it is not, necessarily the most suitable with respect to leakage of activity



Fig. 2. The roentgen instrument with exposure mechanism and one type of collimator

*The roentgen unit.* The silver wire with the radioactive deposit was mounted in a cavity made in a brass rod (see Fig 1) which was inserted in a cylinder of gold serving as shielding material for the radiation. The brass rod could be moved forth and back in the gold shielding The non-exposure and exposure positions of the unit are indicated in the middle and lower parts, respectively of Fig 1 The exposure position of the radiation source is accomplished by means of a photographic shutter release cable (see Fig 2) a spring serving to bring the source back into the non-exposure position. The aperture in the gold cylinder was covered with 1 mm of plastic material to absorb electrons and soft roentgen rays.

*Leakage of radio-iodide* The authors have not tested whether the epoxy resin covering the radioactive deposit is totally impermeable to radio-iodide. However a smear test on the outside of the roentgen unit revealed no activity half a year after it had been loaded with the 250 mCi source mentioned above.

*The spectral distribution of the electromagnetic radiation from the radiation source* The spectral shapes of the radiation from some conventional roentgen tubes have been given by HETTINGER & STARFELT (1958) With the tube running at 45 kV the spectrum showed the highest intensity in the region 20 to 30 keV while at 75 kV the intensity peak was found to lie at 30 to 35 keV (Fig 3) Only inherent filtration was used.

The spectrum shape of the radiation from a 4 mCi $Ag^{125}I$ source of the type described above was analysed by means of a NaI(Tl) scintillation detector Curve I of Fig 4 represents the pulse height distribution, as registered without corrections for the known deviations from a linear relation between pulse amplitudes and absorbed energy in this region (HETTINGER & STARFELT 1958)

Although the fair resolving power of such a spectrometer does by no means

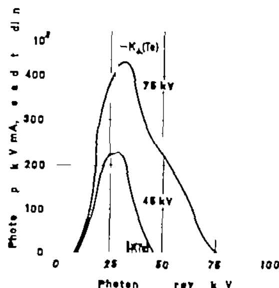



Fig 3 Spectral shape of the radiation from a tube running at 75 kV and 45 kV (from HETTINGER and STARFELT 1958) The energy lines of highest intensity and highest energy respectively of ¹²⁵I are indicated.

permit a resolution of the spectral lines of the radiation the energy level of the $^{125}$I source in relation to conventional roentgen tubes is evident from a comparison between Figs 4 and 3

*Since for many applications the secondary roentgen radiation from the silver* of the source may be disadvantageous an attempt was made to estimate its relative intensity A spectrum of the pure $^{125}$I radiation was therefore registered from a dilute aqueous solution of Na I contained in a small plastic ampoule This spectrum was normalized by subjective judgment to equal the pure $^{125}$I contribution to curve I Fig 4 The normalized $^{125}$I spectrum is shown as curve II and the difference between curves I and II as curve III in Fig 4 Curve *III* should therefore correspond in magnitude as well as in distribution to the secondary radiation from the silver of the source

A silver roentgen spectrum was obtained by placing a silver absorber transmitting less than 0 1 % of the 27 4 keV radiation between the Ag $^{125}$I source and the detector The spectrum thus obtained fitted fairly well to curve III of Fig 4

By proper application of the absorption coefficients of 27 4 keV and 22.2 keV and the absorber thicknesses (air and detector wall) the K radiation from silver was calculated as constituting 10 per cent or slightly less of the total *registered intensity of the Ag $^{125}$I source*

The total amount of AgI deposited on the 0 5 mm hemisphere was in this case 27 μg corresponding to 250 mCi of carrier free Ag$^{125}$I It may be assumed from the current yield for deposition of AgI which was of the order of 60 per cent that other silver compounds were also deposited The amount of silver

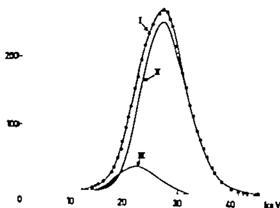



Fig 4 Spectrum shapes of the radiation from 4 mCi Ag$^{125}$I source (curve I) and from $^{125}$I (curve II) as obtained by 3 × 3 NaI(Tl) aluminium canned scintillation detector (Harshaw) and multichannel analyser (Hutchinson Scarrot type) The energy scale was obtained by simple, linear extrapolation through the peaks t 122 keV ($^{57}$Co) and 32 keV ($^{137}$Cs) Curve II was normalized, after subtraction from I to give the secondary source radiation in curve III




Fig 5. Pin-hole images of the radiation source. ) The hemispherical source seen long its axis of symmetry b) Side view

deposited in this source might therefore correspond to 400 mCi of chemically pure carrier free Ag$^{125}$I

The AgI K radiation from sources of this size should therefore be below 10 -o of the total source intensity for all sources weaker than 400 mCi, provided that the $^{125}$I activity is carrier free and no co-deposition of other silver compounds occurs.

*The distribution of the active deposit* Two pin-hole roentgenograms in Fig 5 indicate the distribution of the radioactive deposit of the 250 mCi source. The hemispheric source is seen both along its axis of symmetry (a) and from one side (b)

The pin-hole camera was made of 0 1 mm platinum and the pin-hole by means of an electron beam welding machine (Zeiss) A microscopic inspection revealed an elliptic cross-section of diameters 0.01 and 0 02 mm. The pin-hole

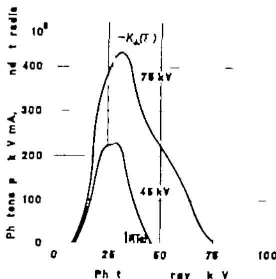



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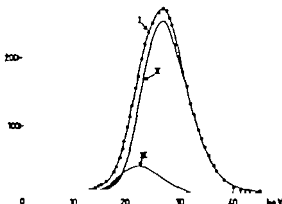



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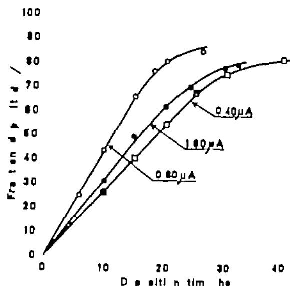



Fig 6. Anode deposition of copper iodid on copper electrodes from aqueous solutions of 0 0002 M NaI and 0 0002 M $Na_2S_2O_3$. Electrode area: 0 8 mm² Solution volume: 1 ml. Stirring rate 400 rpm Fraction of total iodide deposited versus electrolysis time.

images show that the activity is rather uniformly distributed on the source surface

As already mentioned the diameter of the silver wire base of the radiation source was about 0 5 mm. By measuring the pin hole image it was found that the diameter of the active deposit was 0 46 mm. The following formula (see KUNTKE 1957) was used for the calculation

$$S = \frac{a}{b} A - \left(1 + \frac{a}{b}\right) D$$

where $S$ = diameter of the radiation source $A$ = diameter of the pin hole image $D$ = diameter of the pin hole $a$ = distance between radiation source and pin hole $b$ = distance between pin hole and film The ratio between $a$ and $b$ was 1/3

*Cu $^{131}$I as a point roentgen source* Copper would be for two reasons, a better backing material for the deposit than silver as pointed out in part I (BERONIUS et coll 1964) First the self absorption of the roentgen rays is less in copper iodide than in silver iodide. Secondly the secondary radiation produced in copper is of lower intensity and has a lower energy than the secondary radiation from silver The secondary radiation of copper is therefore more easily attenuated to a negligible level

Some tracer experiments were carried out to test the possibility of concentrat

ing iodide anodically on copper with reasonable yield of the halide. The depositions were made from initially neutral aqueous solutions (the electrolyte becomes alkaline during electrolysis because hydroxide is generated at the cathode) containing 0.0002 M of NaI, 0.0002 M of $Na_2S_2O_3$ and a little of $^{125}I$ as a radioactive indicator. (Since commercially available iodine isotopes are delivered in solutions containing a reducing agent such as $Na_2S_2O_3$, this salt was added to test whether it inhibits the formation of halide.) — One milliliter of such a solution was used in each experiment.

A small glass beaker of 16 mm inner diameter served as an electrolytic cell. The electrolyte was stirred at a rate of 400 revolutions per minute by means of a magnetic stirrer; the teflon-coated stirring rod was 12 mm long and 8 mm in diameter.

The flat end surface of a copper wire (Ø = 1 mm) constituted the anode. The cylindrical surface of this wire was coated with wax, the wire being placed vertically at a distance of about 1 mm from the wall of the cell.

A thin platinum wire was used as cathode. Only a small part of this was exposed to the solution to prevent significant sorption of iodide.

The electrolysis was carried out at constant current strength. By measuring the activity of the solution at different times the course of the deposition could be followed. In these tracer experiments the radioactivity was measured by means of a scintillation counter, the detector of which was a 3" × 3" well type NaI(Tl) crystal. The well diameter was large enough for insertion of the electrolytic cell.

The fraction of iodide deposited has been plotted in Fig. 6 as a function of time for three different currents, viz. 0.40, 0.80 and 1.60 μA, corresponding to 50, 100 and 200 μA $cm^{-2}$ respectively. Of these current densities 100 μA $cm^{-2}$ gave the highest deposition rate when the yield of copper iodide was 85 % after 26 hours deposition. The amount of halide deposited, 0.17 micro-moles, corresponds to 0.37 curie of carrier-free $Cu^{125}I$.

It is calculated from the data in Fig. 6 that the initial current efficiencies at the different currents investigated, 1.60, 0.80 and 0.40 μA, amount to 10, 30 and 40 % respectively. The formation of $Cu_2O$ could explain why the current efficiencies are so low.

A few experiments were also undertaken with pure sodium iodide solutions, i.e. omitting the thiosulphate. The results were identical with those obtained when the reducing agent was present, thus indicating that the thiosulphate was not responsible for the low current efficiencies.

The results of this preliminary investigation indicate that $Cu^{125}I$ roentgen sources of the order of one curie may be produced, provided that an electrolyte of suitable composition can be prepared.

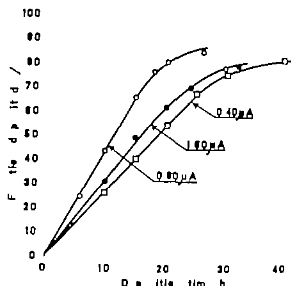



Fig 6. Anode deposition of copper iodide on copper electrodes from aqueous solutions of 0 0002 M NaI and 0 0002 M $Na_2S_2O_3$. Electrode area: 0.8 mm Solution volume 1 ml. Stirring rate: 400 rpm. Fraction of total iodide deposited versus electrolysis time.

images show that the activity is rather uniformly distributed on the source surface

As already mentioned the diameter of the silver wire base of the radiation source was about 0 5 mm By measuring the pin hole image it was found that the diameter of the active deposit was 0 46 mm The following formula (see KUNTKE 1957) was used for the calculation

$$S = \frac{a}{b} A - \left(1 + \frac{a}{b}\right) D$$

where $S$ = diameter of the radiation source, $A$ = diameter of the pin hole image, $D$ = diameter of the pin hole $a$ = distance between radiation source and pin hole $b$ = distance between pin hole and film. The ratio between $a$ and $b$ was 1/3

*$Cu^{131}I$ as a point roentgen source* Copper would be for two reasons a better backing material for the deposit than silver as pointed out in part I (BERONIUS et coll. 1964) First the self absorption of the roentgen rays is less in copper iodide than in silver iodide Secondly the secondary radiation produced in copper is of lower intensity and has a lower energy than the secondary radiation from silver The secondary radiation of copper is therefore more easily attenuated to a negligible level

Some tracer experiments were carried out to test the possibility of concentrat

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# INTRACAVITARY IRRADIATION IN TREATMENT OF CARCINOMA OF CERVIX WITH PARAVAGINAL EXTENSION

by

H. L. KOTTMEIER and R. WALSTAM

Irradiation is the preferred initial treatment at Radiumhemmet for cases of carcinoma of the cervix. A combination of intracavitary radium application and external irradiation has generally been used with the aim of giving a sufficiently high dose to the growth without causing irreparable damage to normal tissue.

Special attention has been directed to the risk of radiation damage to the rectum and the bladder particularly in those cases where the tumour extends to the paracervical or paravaginal tissues. Dose distribution studies on human subjects and on phantoms (KOTTMEIER 1951, WALSTAM 1954) have revealed that the intrauterine radium makes a greater contribution to the dose in the paracervical tissue than the vaginal radium, while the reverse is true for the paravaginal tissue. Experience has shown that an increase of the dosage from the radium inserted into the cervical canal has improved the cure rate in cases of endocervical carcinoma and of paracervical extension (KOTTMEIER 1964)

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## Acknowledgements

The authors are indebted to Prof Ole Lamm and the Swedish Atomic Energy Company for placing laboratory facilities at their disposal, to Dr Roland Christell of the Isotope Techniques Laboratory for performing the spectrometric measurements, to Mr Christer Söremark for technical assistance and to Prof. Torbjörn Westermark for valuable help with the manuscript.

## SUMMARY

The preparation of point $Ag^{125}I$ roentgen sources by the electrolytic deposition of $^{125}I$ on silver micro-electrodes in the development of light portable roentgen units is described.

## ZUSAMMENFASSUNG

Die Herstellung von punktförmigen Strahlenquellen durch electrolytische Ablagerung von $^{125}I$ auf Silbermikroelektroden für leichte, transportable Röntgenapparate wird beschrieben.

## RÉSUMÉ

Les auteurs décrivent la préparation de sources ponctuelles de rayons röntgen en $Ag^{125}I$ par dépôt électrolytique de $^{125}I$ sur des microélectrodes d argent, sources destinées à l équipement d appareils de radiographie portatifs légers.

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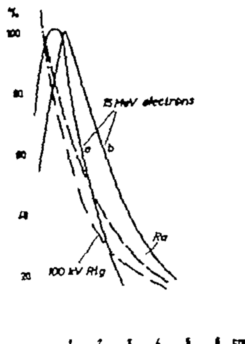



Fig. 4 Comparison between the relative depth dose in the principal plane for the irradiation techniques illustrated in figs 1, 2 and 3.

factory The dose distribution figures for this technique, used for comparison in this paper with our own values, are obtained from the publications by Kepp

*Intravaginal radium* application with the aim of improving the dose distribution in the paravaginal tissue has frequently been employed at Radiumhemmet. A number of irradiators of various lengths, diameters and radium distributions, have been used (Kottmeier 1953) Our interest has also been directed to the value of $^{137}$Cs and $^{192}$Ir as radiation sources for intravaginal gamma irradiation. Results from primary investigations and the advantages envisaged with these medium energy gamma emitters have recently been published (Kottmeier & Walstam 1963)

The interstitial application of radium needles or radioactive colloidal gold was tried in several cases in the years between 1940 and 1946. Although a cure was sometimes achieved, the results were in general unsatisfactory

*Electron beam* irradiation became available at Radiumhemmet in 1957 when a 17 MeV betatron (Siemens) was installed. Intravaginal applications can

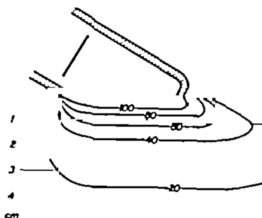



Fig. 1

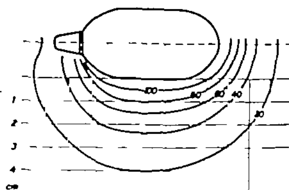



Fig. 2

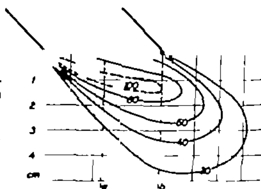



Fig. 3

Fig. 1. Dose distribution in a principal plane for an intracavitary roentgen tube working at 100 kV (according to KEPP).

Fig. 2. Dose distribution around a cylindrical radium applicator.

Fig. 3. Dose distribution in a principal plane for an oblique intracavitary electron tube at 15 MeV.

An increase of the dosage from the radium applied in the vagina in cases of paravaginal extension is generally impossible due to the risk of overdosage and consequent severe damage to the rectum.

The development of *improved external irradiation techniques* has made it possible to obtain better dose distribution in the paracervical and paravaginal tissues. In order to make full use of the advantages both of the improved external irradiation techniques and the various intracavitary irradiation methods, a combination of these is generally used. A detailed knowledge is required of the dose distribution both from the intracavitary and from the external irradiation to obtain the intended tumour dose and to avoid undesired radiation reactions.

*Intravaginal roentgen* techniques were worked out during the decade of 1940 especially in Germany and several papers on this subject have been published. KEPP (1951) developed such a technique and described its clinical applications. At Radiumhemmet intravaginal roentgen therapy has been administered only in a selected number of cases and the results have been unsatis-

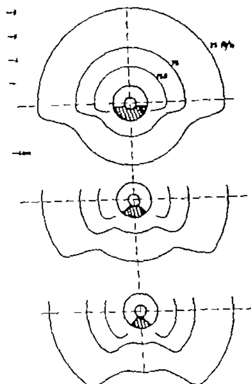


Fig. 6. Shielding effects obtained by supplying cylindrical applicator with various sectors of lead.

The dosage was based on ionization chamber measurements with a special group of Bg-chambers (SIEVERT 1952) and a Victoreen chamber. The chambers on comparison with a sub-standard chamber (THORAEUS 1957) exhibited a small energy dependence in the HVL region from 0.1 to 14.5 mm Cu. The radiation exposure was expressed in terms of a provisional unit, $R_{\mu}$, obtained by using the $^{60}$Co calibration factor for the chambers.

The depth doses in the central cross-section perpendicular to the surface of the applicator or the tube openings are summarized in Fig. 4. Regarding the electron beam, the distribution being more irregular, the depth dose is drawn in two sections, *a* and *b*, the positions of which are illustrated in Fig. 3. As shown in Fig. 4 the electron beam gives in this cross-section the highest dose at a depth of 1 to 2 cm and a low surface dose. The other two techniques are characterized by high surface doses and a rather steep dose fall-off in the first

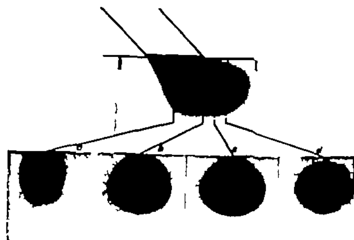


Fig 5 Dose distribution in fou sections, perpendicula to the principal plane f th 15 MeV electron beam, illustrated by photographic ethod

also be performed with this apparatus due to its small size and great mobility Among the standard tubes for the apparatus a tube with an oblique beam aperture has proved particularly suitable for intravaginal irradiation This technique, using 15 MeV electrons has been used in the last few years in 31 selected cases.

In the present communication the dose distributions obtained with the various intracavitary irradiation techniques mentioned above are compared and their relative merits discussed on the basis of the experiences gained in this clinic with electron beam irradiation

## Dose distribution studies

A comparison between the dose distributions for the three irradiation techniques can be made in the diagrams of Figs 1 2 and 3 which give the dose distributions in a central cross section for each of the three methods In Figs 1 and 2 the dose distribution is expressed as a percentage of the dose at 5 mm tissue depth and in Fig 3 as a percentage of the maximum dose

The distribution in Fig 1 was obtained by calculation from data given by KEPP for a particular roentgen tube working at 100 kV The dose distribution around the radium applicator containing 150 mg radium (Fig 2) was obtained by measurements with an automatic isodose recorder (LARSSON LIDÉN & STARFELT 1963) The dose distribution measurements on the electron beam (Fig 3) were performed by using a thin emulsion film (Gevaert Dipos N 51) applied in a tissue-equivalent phantom (mix D) The film density was determined by means of an optical densitometer connected to a semi automatic recording device and calibrated by comparison with ionization chamber measurements.

clinical examination. The positioning of the tube aperture towards the growth can be checked by palpation and inspection. The application of the tube has not caused the patients much discomfort. A total of 3 500 to 4 500 $R_p$ (maximum exposure of Fig 3) has been administered in irradiations with 400 to 500 $R_p$, every day or every second day

Eleven out of 18 patients who received the intravaginal electron irradiation, in addition to the standard radiation technique, are living without any evidence of disease 3 to 6 years after initial irradiation. No improvement was seen in 3 patients. In the remaining 4 patients primary healing of the carcinoma was achieved but the patients died later from pelvic recurrences. A slight late radiation reaction has occured in 3 patients and a vesico-vaginal fistula in one patient with a stage III carcinoma it may be questioned whether the fistula was due to the radiation or to the electrosurgery which was performed later

Intravaginal electron therapy has also been tried as mentioned, in 13 patients with recurrences in the paravaginal tissue in the period 1957—1961 The technique applied was similar to that just described. The authors did not anticipate any permanent healing effect from this irradiation. All these patients have succumbed to the cancer but some improvement was achieved in two of them.


## SUMMARY

Various methods for improving the dose distribution to the paravaginal tissue in the irradiation of carcinoma of the cervix are discussed and comparison is mad between them. An intravaginal electron beam irradiation technique has been tried during 5-year period, with encouraging results, in 31 selected patients with carcinoma of the cervix with paravaginal extension.

## ZUSAMMENFASSUNG

Verschiedene Methoden zur Verbesserung der Dosisverteilung im paravaginalen Gewebe bei der Strahlenbehandlung des Cervix-Carcinomes werden besprochen und verglichen. Eine Behandlungsmethode mit einem intravaginalen Elektronenstrahlenbündel wurde an 31 ausgewählten Patientinnen mit Cervixcarcinom mit paravaginaler Ausbreitung während einer Periode von 5 Jahren mit ermutigenden Resultaten angewandt.

## RÉSUMÉ

Les auteurs étudient et comparent diverses méthodes destinées à améliorer la distribution de dose au tissus paravaginaux dans l'irradiation du cancer du col de l utérus. Ils ont essayé pendant une période de 5 ans, avec des résultats encourageants, sur 31 malades sélectionnées atteintes de cancer du col avec extension paravaginale, une technique d'irradiation intravaginale par un faisceau d'électrons.

centimetres of irradiated tissue In clinical application it is not enough to consider the depth dose or the dose distribution in a central cross-section the three-dimensional dose distribution must be taken into account

The dose distribution around a vaginal cylinder of the type demonstrated in Fig 2 is symmetrical around the axis of the cylinder and thus fully determined by the isodose diagram given in the figure The three-dimensional dose distribution when using the other two techniques, requires more information than given in Figs 1 and 3 An example of such information, obtained by a photographic method is illustrated in Fig 5 It is obvious from this figure that only a small volume can be homogeneously irradiated with this technique It is therefore important that such a technique be applied only on carefully selected patients. Similar considerations are valid also for the intracavitary roentgen irradiation technique

If the tumour mass involves greater parts of the vaginal wall than can be successfully irradiated with the other methods intracavitary irradiation with a suitable gamma applicator might be considered Compared with the other techniques the radium application has the disadvantages of causing considerable radiation protection problems and giving approximately the same radiation intensity in directions where the irradiation should be kept to a minimum. A significant reduction of the radiation can be obtained by employing screens of heavy metals, a condition that may be further improved by using artificial isotopes (KOTTMEIER & WALSTAM 1963) In Fig 6 examples are given of the dose distribution that can be obtained by supplying an applicator of the type shown in Fig 2 with various sectors of lead and using [illegible]Cs as the radiation source It is obvious from these diagrams that the dose may be significantly reduced in some directions i e towards the bladder and the rectum so that a kind of beam irradiation can also be obtained with this technique The application may easily be performed by using an afterloading technique, possibly remotely controlled as described by WALSTAM (1962) and thus considerably reducing the radiation protection problems

## Clinical experience

Intravaginal electron beam irradiation has been administered in addition to the standard radiation therapy in 18 cases of carcinoma of the cervix, stages II and III in the period between 1957 and 1961 and this irradiation technique has also been tried in 13 cases of recurrences following previous irradiation of a cervical carcinoma Cases of clinically defined paravaginal extension of the growth have been selected for this trial A tube with an oblique 24 by 34 mm beam aperture has been inserted into the vagina after careful

FROM THE DIVISION OF RADIOBIOLOGY (DIRECTOR: DOCENT A. NELSON) RESEARCH INSTITUTE OF NATIONAL DEFENCE, SUNDBYBERG, SWEDEN

# EFFECTS OF CONTINUOUS IRRADIATION DURING GESTATION AND SUCKLING PERIODS IN MICE

by

C. Rönnbäck

A definitive number of oocytes is formed in female mice before birth and any reduction in that number cannot be replenished in adults, two facts that make the consequences of radiation injury at the cellular level most serious. It is therefore of interest to examine the radiosensitivity of female mice both in the foetal stage with the DNA-synthesis occurring mainly on the 13th 14th and 15th day of embryonic life (Peters et coll. 1962) and during the first weeks after birth when the ovaries contain oocytes in the sensitive stages of pachyten and early diplotene (Peters 1961)

A relationship between (1) number of oocytes surviving exposure to roentgen irradiation, (2) dose of irradiation, and (3) time elapsing after exposure has been established by Mandl (1959) who stated that the speed with which an individual oocyte disappears seems to be largely independent of the dose of irradiation.

Russell et coll. (1960) reported that continuous irradiation during the first two weeks after fertilization had no ill-effect except for a shortening of the breeding period of females, and also that the total frequency of cell killing from protracted irradiation was smaller than from acute irradiation. Their studies

*Submitted for publication 12 October 1964.

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T ble 1 (cont.)

birth and weaning (mean ± SE)

Series A—2

| IR/IR | IR/C | C/IR | C/C |
|---|---|---|---|
| 5 80 ± 0.42 | 6 24 ± 0.33 | 6.09 ± 0.29 | 6.31 ± 0.22 |
| (20) | (21) | (33) | (35) |
| 5 47 ± 0 46 | 6.13 ± 0 24 | 5.90 ± 0.25 | 5.81 ± 0.25 |
| (17) | (16) | (29) | (32) |
| 102 | 101 | 184 | 206 |
| 93 | 99 | 171 | 186 |
| 8 8 | 2.0 | 7 1 | 9 7 |

after fertilization under these circumstances would have been irradiated before any cleavage movements had occurred. Even at this low level of exposure the first cleavage was delayed. The percentage of intrauterine deaths and resorptions was 5 7 % in the controls as compared to 15 % among the irradiated animals.

An extreme sensitivity of the ovaries even to low dose rates during the second week after birth has been reported by RUGH et coll. (1959) A total dose of 85 R given continuously during one week (12 2 R/day) caused sterility after the production of either a single litter or a second litter of reduced size. This sensitivity rapidly diminished with age

OAKBERG (1960) has stated that during the second postnatal week the majority of the oocytes are in stages that have an extremely high radiation sensitivity with an $LD_{50}$ of about 9 R.

The purpose of the present investigation has been to study the effects on fertility of γ-irradiation given at a low dose rate to females of the inbred CBA mouse strain in the foetal stage and/or to young suckling females.

*Materials and Methods* Inbred CBA mice were used in the experiment. The females were about 70 days at mating and were controlled daily for vaginal pl g Th pregnant animals were divided into two groups one of which served as a control and the other as an irradiation group The latter was then placed in the irradiation field. If gestation is assumed to begin on the morning

Table 1

*Number of litters and litter size at*

Series A—1

| | IR/IR | IR/C | C/IR | C/C |
|---|---|---|---|---|
| *Mean litter size* (total) | | | | |
| (1) at birth | 5.83 ± 0.36 (23) | 5.52 ± 0.38 (21) | 6 11 ± 0 26 (28) | 6.50 ± 0.32 (32) |
| (2) at weaning | 5 78 ± 0.36 (18) | 5.58 ± 0.35 (19) | 5.85 ± 0.28 (26) | 6.54 ± 0.33 (28) |
| *Litters with at least one alive at weaning* | | | | |
| Number of young | | | | |
| (1) t birth | 112 | 106 | 157 | 191 |
| (2) at weaning | 104 | 106 | 152 | 184 |
| Loss in per cent | 7 1 | 0 | 3.2 | 3 7 |

indicated clearly that continuous $\gamma$-radiation cannot be compared with the same radiation administered at a specific stage in the process of embryogenesis.

STADLER & GOWEN (1962) observed among mice of several strains irradiated throughout their lifetimes with gamma rays from $^{60}$Co that 12 R per day resulted in sterility and loss of the germ line they stated that dosages between 0 6 and 2 0 R/day permitted sufficient reproduction to continue the germ line for at least fourteen generations

BROWN et coll (1963) continuously irradiated female albino rats at different dose rates, between 2 and 20 R/day and found no significant alteration in litter size in the first four litters born to females placed in the radiation field at the time of conception The litters born subsequent to the fourth one decreased in size

According to PETERS (1963) the response to a small dose of radiation is not uniform but varies considerably according to the age of the animal irradiated. The younger the animal the higher the proportion of eliminated oocytes. The reproduction performance of female mice was investigated by irradiating them with a single dose of 20 R roentgen at varying times from birth to seven weeks of age A definite reduction in the total reproductive capacity was observed in all the groups irradiated and only one of them produced the normal number of young

RUGH & GRUPP (1961) exposed pregnant mice to roentgen irradiation so that 5 R were absorbed by the embryos 0 5 days after conception The eggs

Table 1 (*cont.*)

*birth and weaning* (*mean* ± *SE*)

Series A—2

| IR/IR | IR/C | C/IR | C/C |
|---|---|---|---|
| 5.80 ± 0.42 | 6.24 ± 0.33 | 6.09 ± 0.29 | 6.31 ± 0.22 |
| (20) | (21) | (33) | (25) |
| 5.47 ± 0.46 | 6.13 ± 0.24 | 5.90 ± 0.25 | 5.81 ± 0.25 |
| (17) | (16) | (29) | (32) |
| 102 | 101 | 184 | 206 |
| 93 | 99 | 171 | 186 |
| 8.8 | 2.0 | 7.1 | 9.7 |

after fertilization under these circumstances would have been irradiated before any cleavage movements had occurred Even at this low level of exposure the first cleavage was delayed The percentage of intrauterine deaths and resorptions was 5.7 % in the controls as compared to 15 among the irradiated animals.

An extreme sensitivity of the ovaries even to low dose rates during the second week after birth has been reported by RUSSELL et coll. (1959) A total dose of 85 R given continuously during one week (12.2 R/day) caused sterility after the production of either a single litter or a second litter of reduced size. This sensitivity rapidly diminished with age.

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*Materials and Methods* Inbred CBA mice were used in the experiment. The females were about 70 days at mating and were controlled daily for vaginal plug The pregnant animals were divided into two groups one of which served as a control and the other as an irradiation group. The latter was then placed in the irradiation field If gestation is assumed to begin on the morning

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| (2) at weaning | 5.78 ± 0.36 (18) | 5.58 ± 0.35 (19) | 5.85 ± 0.28 (26) | 6.54 ± 0.33 (28) |
| *Litters with at least one alive at weaning* | | | | |
| Number of young: | | | | |
| (1) at birth | 112 | 106 | 157 | 191 |
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| Loss in per cent | 7.1 | 0 | 3.2 | 3.7 |

indicated clearly that continuous $\gamma$-radiation cannot be compared with the same radiation administered at a specific stage in the process of embryogenesis.

STADLER & GOWEN (1962) observed among mice of several strains irradiated throughout their lifetimes with gamma rays from $^{60}$Co that 12 R per day resulted in sterility and loss of the germ line, they stated that dosages between 0.6 and 2.0 R/day permitted sufficient reproduction to continue the germ line for at least fourteen generations.

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RUGH & GRUPP (1961) exposed pregnant mice to roentgen irradiation so that 5 R were absorbed by the embryos 0.5 days after conception. The eggs

Table 3

*Fertility test uterine analyses of irradiated females (A-2)*
$\chi = 0.87$ $DF = 1$ ($p = 0.30$)

| Series | Living foetuses | Intrauterine death |
|---|---|---|
| IR/IR | 0 | — |
| IR/C | 6.83 ± 0.25 (35) | 19/258 (7.35 %) |
| C/IR | 0 | — |
| C/C | 6.68 ± 0.17 (37) | 15/262 (5.73 %) |

The actual doses received by the four groups of animals by the end of the suckling period were IR/IR—338 R IR/C—164 R C/IR—174 R C/C—0 R.

The fertility of the matured animals from the four groups was tested by mating one untreated male and one female from each of the four groups being placed in the cages. The experiment, due to limited facilities, was conducted in two successive identical repetitions, here called A 1 and A 2.

In the A 1 series, the females were allowed to give birth to their litters. The number of pregnant females, the litter size at birth and the juvenile deaths were recorded. The females in the second series (A 2) were killed on the 18th day of gestation and the uteri were analysed.

The fertility of a small group of males from series A 1 was also tested by mating them to normal females, two females for each male. These females were also sacrificed.

## Results

Table 1 gives the litter size at birth and at weaning and the number of litters for the different irradiation groups. Using the litter size as a measure, no statistical differences were found between the four groups or between the two experiments.

It may also be seen from this table that the loss of young in litters with at least one alive at weaning was not affected by the irradiation. The numbers in IR/IR in both the A-1 and A 2 series are somewhat higher but they do not exceed the high value of the control group in series A-2.

The fertility of the mature female offspring was tested by mating them to untreated males, as mentioned above. The results from A 1 where the litters were born, are presented in Table 2 and the results of the uterine analyses in

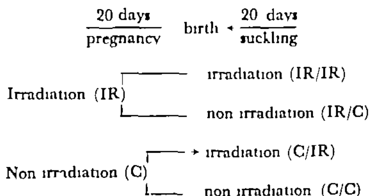
**Table 2**

*Fertility test number of litters born to irradiated mothers (A 1) IR/C versus C/C. t = 1 69* ($p > 0\ 05$)

| Series | Litter size $\bar{x} \pm SE$ |
|---|---|
| IR/IR | 0 |
| IR/C | 5 17 ± 0 17 (47) |
| C/IR | 0 |
| C/C | 4 63 ± 0.27 (38) |

after the insemination of the female the irradiation of the zygote starts within the first 12 hours of its life

The radiation facility consisted of a cesium 137 source of 25 Ci in front of which two racks accomodated eighteen cages each The distance between the midline of the cages and the source was about 4 meters i e a position where the midline dose rate was 8 4 R/day to give a dose of about 170 R per 20 days. The dose rate was measured in air by an ionizing chamber (Philips ionizing chamber type 37488/10 HVL 0 07 to 2 mm Cu) placed horizontal and perpendicular to the direction of the beam 1 0 meter above the floor the same height as the cesium source during irradiation The ionizing chamber was connected to a Philips Universal dosemeter of type 37470 The irradiation was administered continuously except for a small period each day during which the animals were cared for After the first twenty days, i e at birth the two main groups of irradiated (IR) and non irradiated (C) animals were divided into two subgroups according to the scheme below



No hypersensitive period was detected with a dose rate of 8 4 R/day during the twenty days of foetal development. On the other hand, the same dose rate given during the first twenty days post partum caused an irreversible sterility in the young females, which seems to agree with OAKBERG's findings of an $LD_{50}$ of 9 R for oocytes during the second week.

Irradiation of the males with the dose rate mentioned produced no effect on their fertility

Further investigations have now been performed with irradiation during certain periods of the first twenty postnatal days and the results will be published shortly

## Acknowledgement

The author wishes to express his sincere thanks to Professor K. G Luning for his interest in the work.

## SUMMARY

CBA mice have been irradiated with γ-rays at low dose rate from a cesium source during the foetal stage and the suckling period. Females that received 170 R during the suckling period were sterile but those irradiated as foetuses were not. Irradiated males exhibited no decrease in fertility

## ZUSAMMENFASSUNG

CBA Mäuse wurden bei niedriger Dosisleistung mit γ-Strahlen aus einer Cs-Quelle bestrahlt, sowohl im foetalen Stadium als auch während der Säuglingsperiode. Weibliche Mäuse, die 170 R während der Säuglingsperiode erhalten hatten, waren steril, aber jene, die während des Foetalstadiums bestrahlt wurden, waren nicht steril. Männliche Mäuse zeigten keinerlei Verminderung der Fruchtbarkeit.

## RÉSUMÉ

Des souris CBA ont été irradiées à faibl débit de dose de rayonnement gamma d Cs pendant la période foetale et pendant la périod ou elles étaient allaitées. Les femelles qui avaient reçu 170 R pendant la période d'allaitement furent stériles alors que celles qui avaient été irradiées pendant la période foetale ne le furent pas. Les mâles irradiés n ont pas présenté de diminution de leur fertilité.

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**Table 4**

*Fertility test of irradiated males* $\chi^2 = 6.84$ $DF = 3$ $(0.10 > p > 0.05)$

| Series | No. of males tested | Pregnant females ( ) mated | Intrauterine deaths |
|---|---|---|---|
| IR/IR | 48 | 85.4 | 59/578 (10.21 %) |
| IR/C | 45 | 81.1 | 39/507 (7.69 ) |
| C/IR | 78 | 81.0 | 61/850 (7.53 %) |
| C/C | 81 | 85.2 | 90/936 (9.62 ) |

A 2 are given in Table 3. These tables make it clear that a dose of 170 R during the suckling period caused complete sterility in the young females. The same dose administered during the gestation time had no effect on the fertility of the young when examining only the first litter from the irradiated females. There is no statistical difference between the IR/C group and the controls in either Table 2 ($t = 1.69$, $p > 0.05$) or in Table 3 ($t = 0.50$, $p > 0.05$). The frequencies of intrauterine deaths are also of the same order of magnitude in the irradiation groups and the control, as evident from Table 3 ($\chi^2 = 0.87$, D F = 1, p about 0.30).

The fertility test of the males irradiated in the same way as the females gave quite a different result. No effects of sterility were apparent when the males were tested by means of untreated females (Table 4). The frequencies of pregnant females in the three irradiation groups are similar to that of the control group, and the proportion of dead foetuses is not higher among the irradiated than in the controls. A $\chi^2$ analysis produced no evidence of differences between the four groups.

## Conclusions

Irradiation with 170 R during gestation caused no detectable effects in the first litter. This is in good agreement with the results obtained by RUSSELL (1960) with a dose rate of 87 R/week during the first 14 days of gestation.

Table 1 indicates that no statistical difference in litter size could be demonstrated between the irradiated groups and the controls. As only the first litter from the females was examined, no data are available on the overall productivity of the females in any group.

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# ERYTHEMA DIFFERENCES BETWEEN THE CRANIAL AND CAUDAL PARASTERNAL REGIONS AT 12 MeV ELECTRON IRRADIATION

by

Gustaf Notter, Tassos Thoulias and Per Erik Åsard

Following irradiation of the parasternal region, radiation erythema is often more noticeable in the cranial than in the caudal part of this area even though the treatment of the two areas has been identical (Fig 1)

It has been suggested that the increased sensitivity to ionizing irradiation of the skin on the neck and upper part of the thorax may be attributed to various causes, such as prolonged sensitizing of the skin through exposure to light, differences in the pigmentation of the skin, or various degrees of secondary irradiation of the skin due to variations in the underlying bone tissue. However the same difference in erythema at the level of the second intercostal space is also seen during spontaneous blushing or after rubbing of the skin. The reddening spreads over the face, the neck and a V-shaped area on the upper part of the thorax but not as a rule below the second intercostal space (Fig 2) This limitation is due to a varying sympathetic innervation of the skin at the cervico-thoracic level.

Submitted for publication 4 May 1964.

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Fig. 1. Erythema following irradiation of the supraclavicular and parasternal areas with 12 MeV electrons. Less erythema in lower part of the parasternal region. The shape of the erythema on the left side was caused by rubbing the skin.

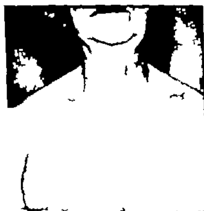


Fig. 2. Spontaneous blushing. Cervico-thoracic limitation of the erythema at the level of the second intercostal space, corresponding to the innervation area of C4 and D2.

Table 1

*Ratio between patients with more extensive radiation erythema at points $a_1$ and $a_r$, as compared with point b and total number of patients measured*

| Significance | Before irradiation | After 5th irrad. | After 10th irrad. | 14 days after last irrad | 28 days after last irrad. |
|---|---|---|---|---|---|
| p = 0 1 | 12/13 | 14/16 | 15/16 | 14/16 | 9/16 |

Table 2

*Ratio between patients with more extensive radiation erythema at point b as compared with point $b_r$, and total number of patients measured*

| Significance | Before irradiation | After 5th irrad | After 10th irrad. | 14 days after last irrad. | 28 days after last irrad. |
|---|---|---|---|---|---|
| p = 0 1 | 4/13 | 7/16 | 7/16 | 7/16 | 4/13 |

Significant difference in dermal erythema at the same level has also been observed by ADAMS-RAY (1952) after irritation of the skin with mustard oil, not only in adults but even in newborns indicating that the difference in sensibility of the skin is congenital and not a result of environmental conditions such as exposure to light or heat

The present study has been made to investigate whether the difference in radiation erythema between the cranial and caudal parasternal regions was influenced by the same mechanism and was a constant phenomenon during and after irradiation

*Material and Methods* Sixteen patients with breast cancer were irradiated on the parasternal region after radical mastectomy with 12 MeV electrons from a Siemens 17 MeV betatron and received 10 × 400 $R_\beta$ in 22 days to 2 fields 6×8 cm (Fig 3) ($R_\beta$ is a provisional unit obtained by using the Co R factor for a 100 R Victoreen chamber for the electron beam)

An erythema developed during treatment and reached its maximum about 14 days after the end of the course, after which it diminished

The differences in skin redness were estimated by measuring the light reflection of the skin in the 550 mμ wavelength range which includes the typical absorption bands of hemoglobin (PFEIDERER 1960) The measuring probe (a commercial unit from AGA) 8 cm high and 7 cm in diameter consists of a light source, a filter holder and a selenium photocell the filter used was of the interference type with a transmission of 500 to 580 mμ (Baltzer s Filtra

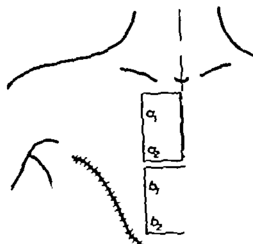



Fig. 3. The two parasternal irradiation fields, and the measuring points $a_{1-2}$ and $b_{1-2}$.

flex K No. 4) The principle in these measurements was that the filtered light beam illuminated an area of skin, 2 cm in diameter whereupon the reflected light activated the photocell, the current produced being measured with a galvanometer (Kipp type A 70)

The difference in skin redness was calculated from $\frac{I - I}{I_b} \times 100\,\%$ where $I_b$ and $I$ are the currents measured at points *b* and *a*, respectively A positive difference indicates that the redness was more marked at point *a* than at point *b* The differences obtained from photoelectric measurements of this type are very slight, even when the visual differences are quite considerable, and for this reason the voltage supply to the measuring apparatus was stabilized

The skin redness was measured at all four points in the irradiated areas (Fig 3) before in the middle of and at the end of the radiation treatment as well as at 14 and 28 days after treatment. On each occasion, 10 readings were taken for each of the four points the average standard deviation being 2 % The statistical significance of the difference of the means between any two points on one and the same patient was estimated with the t-test

## Results

The measurements disclosed no significant differences in skin redness between points $a_1$ and $a_2$. These two points have therefore been combined to a mean value for each patient.

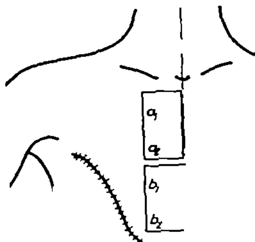



Fig. 3. The two parasternal irradiation fields, and the measuring points $a_{1-2}$ and $b_{1-2}$

flex h. No. 4) The principle in these measurements was that the filtered light beam illuminated an area of skin, 2 cm in diameter whereupon the reflected light activated the photocell, the current produced being measured with a galvanometer (Kipp type A 70).

The difference in skin redness was calculated from $\frac{I_b - I}{I_b} \times 100$ % where $I$ and $I$ are the currents measured at points $b$ and $a$, respectively. A positive difference indicates that the redness was more marked at point $a$ than at point $b$. The differences obtained from photoelectric measurements of this type are very slight, even when the visual differences are quite considerable, and for this reason the voltage supply to the measuring apparatus was stabilized.

The skin redness was measured at all four points in the irradiated areas (Fig. 3) before, in the middle of and at the end of the radiation treatment as well as at 14 and 28 days after treatment. On each occasion, 10 readings were taken for each of the four points, the average standard deviation being 2 %. The statistical significance of the difference of the means between any two points on one and the same patient was estimated with the t-test.

## Results

The measurements disclosed no significant differences in skin redness between points and $a_2$. These two points have therefore been combined to a mean value for each patient.

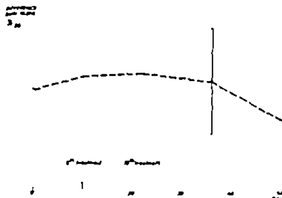


Fig 4 Mean value of differences between the dermal redness at points $a_n$ and $b$ for all patients. The bars indicate the standard deviation of the mean. At the last measurements, when pigmentation of skin develops, the curve is sloping

It is shown in Table 1 that practically all the patients had a significantly stronger redness in the upper field (99 9 % probability) as compared with the lower field points $b_1$ and $b_2$, except for the last measurement 14 days after completing the treatment

It may be seen from Table 2 that only about half the number of patients also had a significantly stronger redness at point $b_1$ as compared with $b_2$. This may depend on point $b_1$ being located near the 2nd intercostal space i e at the level of the cervico-thoracic junction (Fig 3)

The mean values of the differences in dermal redness between the upper field and point $b_2$, for all patients are given in Fig 4 The mean differences seem to be approximately constant throughout the period until the last measurement where the curve is falling Depending on the individual differences between the patients, the standard deviations of the means are of course large

## Discussion

The difference in dermal redness on the neck and above the second intercostal space on the one hand and in the area caudal to this space on the other is most probably due to dissimilarities in the sympathetic innervation of these two regions. The cranial region corresponds to the innervation field of the upper cervical spine C1—C4 with C4 as the lower limit The caudal region is innervated from the upper thoracic spine with D2 as the upper limit C4 receives its vasoconstrictor impulses via the stellate ganglion and the superior cervical ganglion whereas the lower cervical and upper thoracic segments receive theirs from the stellate ganglion and the middle cervical ganglion The thoracic spinal segment is held to have a higher sympathetic tonus causing vasoconstriction and reducing the blood flow This can explain why the erythema in the caudal region is less marked

Most of the patients also received irradiation to the supraclavicular area (see Fig 1) However comparisons between these and patients without such treatment indicated that no contributory dose from this field influenced the erythema in the parasternal field.

As already mentioned, the mean difference in redness was less on the last measurement, 28 days following the radiation therapy (Fig 4) A plausible explanation of this is that 15 to 30 days after the end of the irradiation a slight brown pigmentation developed. This started always in the lower field where the epithelium was less affected than in the upper field. As it is not possible to distinguish exactly between erythema and pigment by means of photometry (TROTSIER 1963) this may have influenced the measurements, causing a higher absorption of light in the lower field, and hence a smaller measured difference between the two fields. Pigmentation was observed visually at the last measurement in four patients, all belonging to the group without difference in redness at the last measurement.


## SUMMARY

Report on results of photometric evaluation of dermal erythema in 16 patients with breast cancer by measurements before during and after irradiation of the parasternal region with 12 MeV electrons, 10 400 $R_\beta$ in 22 days. The erythema, which is chiefly conditioned by the blood circulation, was throughout the period more marked in the region cranial to the second intercostal space, corresponding to the innervation field of the nerves from the cervical spine, with C4 as the lower limit. The differences in the radiation erythema between the regions cranial and caudal t this thoraco-cervical border were significant on all occasions.

## ZUSAMMENFASSUNG

An 16 Patienten mit Brustkrebs wurde das Hauterythem bevor während und nach der Bestrahlung der parasternalen Region mit 12 MeV Elektronen photometrisch gemessen. Die erabreichte Dosis war $10 \times 400$ $R_\beta$ in 22 Tagen. Das Hauterythem war im kranialen Teil der parasternalen Region, oberhalb des 2 Intercostalraumes, entsprechend dem Innervationsgebiete der Cranialnerven 1—4 deutlich starker ausgeprägt als im unteren Bereich der parasternalen Region.

## RÉSUMÉ

L érythème cutané après irradiation de la région parasternale par des électrons de 12 M V été mesuré photométriquement avant, pendant et après l'irradiation, sur 16 malades atteintes de cancer du sein. La dose administrée était de $10 \times 400$ $R_\beta$ en 22 jours. L érythème cutané était nettement plus accusé dans la partie supérieure de la région parasternale au dessus du 2ᵉ espace intercostal, correspondant au territoire des 4 premiers nerfs cervicaux, que dans la partie inférieure de la égion parasternale.

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# DISTRIBUTION OF RADIOSTRONTIUM IN DEVELOPING BONES AND TEETH

## Microautoradiographic study with $^{90}$Sr

by

L. HAMMARSTRÖM, A. NILSSON and S. ULLBERG

Exact knowledge of the distribution pattern of radiostrontium and its alteration with time is essential for the understanding of the complex changes which gradually become manifest in the skeleton as a result of continuous irradiation. Available distribution studies have been based upon impulse counting techniques or autoradiography (PECHER 1941, 1942, COMAR et coll. 1952, KIDMAN et coll. 1952, JOWSEY et coll. 1953, ENGSTRÖM et coll. 1957, OWEN et coll. 1957, DOWNIE et coll. 1959, JEE & ARNOLD 1960, NILSSON & ULLBERG 1962). However, the high-energy radiation of $^{90}$Sr (0.54 MeV for $^{90}$Sr and 2.24 MeV for the disintegration product $^{90}$Y) is not suitable for microautoradiographic investigations. APPELGREN et coll. (1963) in their studies of radiostrontium uptake in osteosarcomas, found that the extranuclear $\beta$ radiation (11.5 keV) of $^{90}$Sr could be utilized for autoradiography. This quality has been taken advantage of in the present study of $^{90}$Sr distribution in young growing rats during the immediate post injection period.

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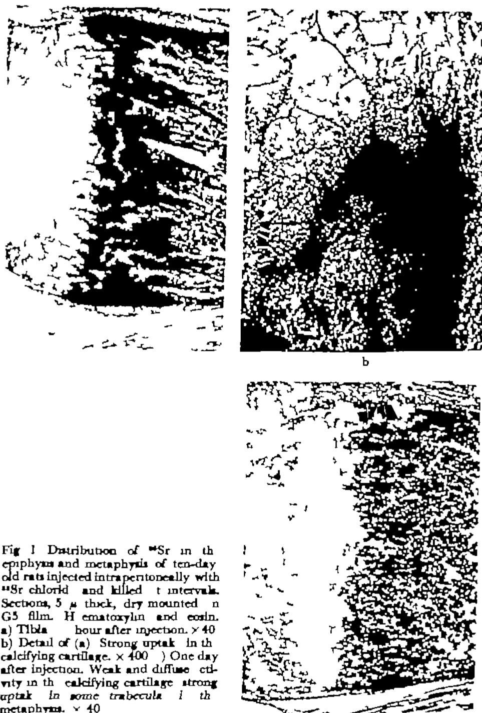



Fig 1 Distribution of $^{89}$Sr in th epiphysis and metaphysis of ten-day old rats injected intraperitoneally with $^{89}$Sr chlorid and killed t intervals. Sections, 5 μ thick, dry mounted n G5 film. H ematoxylin and eosin. a) Tibia hour after injection. × 40 b) Detail of (a) Strong uptak in th calcifying cartilage. × 400 ) One day after injection. Weak and diffuse cti- vity in th calcifying cartilage strong *uptak in some trabecula l th* metaphysis. × 40

*Material and Methods* Ten-day-old albino rats were injected intraperitone ally with 0.25 ml carrier free Sr chloride (Amersham) corresponding to an approximate total dose of 50 μC $^{89}$Sr per animal The animals were killed one

hour and one, two four and sixteen days after the injection of $^{89}$Sr under ether anaesthesia by immersion in a mixture of carbon dioxide and hexane (— 75 C) and the head and a hind leg cut off and embedded in carboxy methyl cellulose Sagittal sections, 5 $\mu$ thick, were taken through these structures using ULLBERG's (1954 1958) technique. The sections were taken on Scotch tape No. 688, dried overnight in a cold room (— 10 C) and mounted on Ilford G5 nuclear emulsion plates with an emulsion thickness of 5 $\mu$ The surface of the emulsion was coated with a thin layer (0 6 $\mu$) of urea alkyd by immersion in a solution of 8 parts acetone, 1 part urea alkyd, and 0.3 parts hardener The hardener consisted of equal parts of ethyl glycol and absolute alcohol to which 1 % HCl was added. (After the addition of the hardener the urea alkyd solution tolerates storage for 24 hours at room temperature before becoming opaque from excessive polymerization.)

The plates after immersion were placed vertically to allow excess fluid to drain off and the solvents to evaporate. The emulsion surface by this stage was dry' and adhesive, and the tape with the sections could be mounted.

The films were exposed under slight pressure for 4 to 7 days, the tape backing then being removed with acetone. A sponge drenched with acetone was pressed against the back of the tape for about 5 min The tape backing consisting of polyvinyl chloride, then separated from the adhesive and was removed with a pair of forceps. (If the tape borders were not evenly cut before the application of the tape, irregularities caused adhesion between the adhesive and the backing of the tape, resulting in the concomitant removal of the sections.) The tape adhesive was then dissolved in xylene within two hours.

After removal of the tape the photographic plates with adhering sections were passed down through an ethyl alcohol series (two minutes in each) developed, fixed and rinsed. The sections adhering to the G5 plates were then stained with haematoxylin and eosin or according to van Gieson's method and mounted under a cover slip with Canada balsam.

## Results

*Bone* The uptake of $^{89}$Sr was greatest in the epiphysis and metaphysis of the long bones one hour after intraperitoneal injection (Fig 1a) The activity was weak and diffuse throughout the epiphyseal cartilage but there was a very strong accumulation of $^{89}$Sr in the zone of calcifying cartilage Activity was also very strong in the primary trabeculae of the metaphysis but declined towards the diaphysis. Not only was the activity marked and diffuse in these regions but there were also a striking number of 'hot spots' near which lines and streaks with high activity between cartilage cells were also evident (Fig 1b)

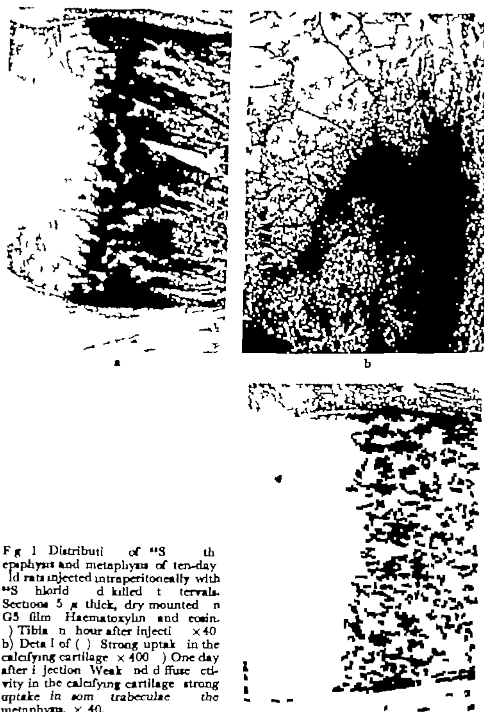



Fig 1 Distributi of $^{90}$S th epiphysis and metaphysis of ten-day ld rats injected intraperitoneally with $^{90}$S hlorid d killed t tervals. Sections 5 μ thick, dry mounted n G5 film Haematoxylin and eosin. ) Tibia n hour after injecti ×40 b) Deta l of ( ) Strong uptak in the calcifying cartilage ×400 ) One day after i jection Weak nd d ffuse activity in the calcifying cartilage strong uptake in som trabeculae the metaphysis. ×40.

*Material and Methods* Ten-day-old albino rats were injected intraperitoneally with 0 25 ml carrier free $^{90}$Sr chloride (Amersham) corresponding to an approximate total dose of 50 μC Sr per animal The animals were killed one

A strong uptake was present in the ossification centres of the epiphysis. In the diaphysis, most of the activity was limited to the periosteum (Fig 2a)

One to two days after injection, the activity in the calcifying cartilage was weak and diffuse and the activity had also decreased in the primary trabeculae adjacent to this zone The activity was still high in the other parts of the primary trabeculae and in the secondary trabeculae but was now more uniformly distributed with fewer hot spots (Fig 1c) Accumulation was evident both on the surface and within the bone tissue of the trabeculae The activity in the periosteum and endosteum had declined but in the cortex it was both strong and diffuse (Fig 2b)

Four to sixteen days after injection the activity in the epiphysis and metaphysis was weak and diffuse Although there were some differences in the degree of activity in different trabeculae there were no hot spots. The uptake of $^{90}$Sr was much greater in the cortex of the diaphysis than in the epiphysis and metaphysis. The diffuse activity declined slowly while the apposition lines with their greater activity became more evident at ever increasing distances from the periosteum (Fig 2c)

*Teeth.* One hour after injection a narrow zone of strong activity appeared in the dentine immediately adjacent to the predentine. There was slight uptake in deeper parts of the dentine (Fig 3) At longer post injection intervals the new dentine formed adjacent to the pulp contained diffusely distributed activity and the strongly active zone was displaced farther and farther from the pulp (Fig 4) The dentine formed prior to injection also had increased diffuse activity (Fig 4b)

In the enamel the distribution pattern one hour after injection differed to a great extent from tooth to tooth and even from cusp to cusp of a particular tooth. Uptake in the lower second molar can serve to illustrate the different phases. Strontium uptake immediately under the high ameloblast layer in the cervical region was moderate in a broad and diffusely demarcated zone (Fig 3c) The height of the ameloblast layer decreases towards the tip of the cusp and in this region there was only slight uptake. A fairly strong uptake of $^{90}$Sr throughout the entire enamel was evident at the tip of the cusp under the low ameloblasts the enamel at this site stained basophilic but was eosinophilic in other regions (Fig 3)

One day after injection these areas could still be easily distinguished but the distribution in the enamel steadily became more homogeneous and the entire enamel stained basophilic (Fig 2 a and b)

Sixteen days after injection there was diffuse uptake in the upper third molar a tooth which at the time of injection had not begun to be mineralized the uptake was much the same in the enamel and dentine.

b



Fig 2 Distribution of $^{35}$S i the tibia of ten-day-old rats injected traperitoneally with $^{35}$S chloride nd killed t intervals. Sections, 5 µ thick, dry mounted on G5 film a) On hour after i ject on. Strong uptak in th periosteum so ewhat less in the endosteum Van Gieso × 40 b) One day after injection Diffuse ti ity throughout the compact bone w th trongest tivity nea th periosteum. H ematoxylin nd eosin. × 40 ) Si teen days after injection. Zon of trong ctiv ty near th endosteum weak nd diffuse activity in the compact bone. H emat xyli nd eosin 80



b

Fig. 4. ) Distribution of $^{89}$Sr in the first upper molar of twelve-day-old rat injected intraperitoneally with $^{89}$Sr chloride two days previously. Section, 5 μ thick, dry-mounted on G3 film. Haematoxylin and eosin. × 30. b) Detail of ( ) 160. Diffuse uptake throughout the enamel; the zone of strong activity in the dentine is now situated at some distance from the pulp diffuse uptake in the dentine formed before and after the injection.




Fig 3 a) Distribution of $^{35}$S n th bud of th lower second molar of ten-day-old rat one hou after traperitoneal njection of $^{35}$S chloride. Sections, 5 μ thick, dry mounted on G5 film Haema toxyli and eosin. × 110 b) Detail of ( ) × 175. ) Deta l of ( ) × 160 Uptak in th enamel is mainly concentrated to the cervical region and t the tip of th usp under th low meloblast layer n the latter the ctivity is spread throughout the enamel Th matrix of the enamel stains basophilic. In the cervical region th ctivity extends bout half way through the matrix. Th high meloblast layer is a sign that matrix formation is taki g place A on of strong activity lies i the dentine djacent to th predentine dent formed pri to th injection has weak nd diffuse activity

## SUMMARY

A method for dry-mounting tissue sections in microautoradiography is described. The distribution of strontium 85 in developing bones and teeth has been studied up to sixteen days after a single intraperitoneal injection in albino rats.



## ZUSAMMENFASSUNG

Eine Methode für die Trockenmontierung von Gewebeschnitten für die Mikro-Autographie wird beschrieben. Die Verteilung von Strontium 85 in wachsenden Knochen und Zähnen wurde an Albinoratten nach einmaliger intraperitonealer Injektion bis zu 16 Tagen verfolgt.



## RÉSUMÉ

Les auteurs décrivent une méthode de montage à sec de coupes de tissues en microautoradiographie. Ils ont étudié la distribution de strontium 85 dans les os en développement et les dents jusqu'à seize jours après une injection intrapéritonéale unique chez des rats albinos.


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## Discussion

The radiation from strontium 85 proved quite suitable for detailed autoradiographic studies of strontium metabolism. The technique used eliminates contact between the tissues and water or other fluids, before exposure so that there is no risk of redistribution or loss of the injected isotope

The strong initial uptake of strontium in the epiphysis and metaphysis was greatest in the calcifying cartilage The marked reduction in this uptake one day after injection illustrates the rapid breakdown of this cartilage in growing bone

Uptake in the diaphysis was initially limited mainly to certain sites but subsequently became more diffuse throughout the cortex This observation supports the assumption of mineral uptake in separate phases (JONES & COPP 1951) However activity remained highest along what represented the earlier apposition lines. The diffuse activity in the cortical bone then slowly declined which probably reflects the slow rate of mineral exchange in this region The initial strong activity in the periosteum sank deeper into the cortex as the time after injection increased and by sixteen days had partially disappeared at the endosteum. This illustrates the classical concept of growth of a long bone periosteal deposition and endosteal resorption

The weak and diffuse uptake of radiostrontium in the dentine laid down before injection and the gradual increase of activity correspond with what has been observed after the injection of ⁴⁵Ca and can probably be associated with the increase in the hardness of dentine in young animals (KUMAMOTO & LEBLOND 1956) Strontium circulating in the blood gave a degree of activity to the dentine formed after injection

The pattern of strontium uptake in the enamel would seem to support DIAMOND & WEINMANN's (1940) theory of phased mineralization The high ameloblast layer in the cervical region is a sign that matrix formation is taking place (ORBAN 1953) the newly formed enamel matrix has a moderate uptake of strontium When the enamel matrix has attained its full thickness the ameloblast layer becomes reduced in height mineral deposition seems to recommence only after this has taken place The later uptake is much greater than that which occurs during the formation of the matrix The change in stainability that was evident during the heavy strontium uptake has previously been studied in decalcified teeth by CHASE (1935) among others He observed this change during the phase of development preceding the appearance of the final fully mineralized enamel His observations seem to fit in with what was seen during the present study The initial distribution pattern persists for a long time after injection but a subsequent uptake of strontium from the circulating blood produces diffuse activity throughout the enamel

FROM THE INSTITUTE OF RADIOPHYSICS (DIRECTOR: PROF. R. SIEVERT), KAROLINSKA SJUKHUSET, STOCKHOLM, SWEDEN

# EXIT DOSE MEASUREMENTS IN COBALT 60 TELETHERAPY

by

LENNART SUNDBOM

A suitable irradiation technique in radiotherapy is generally worked out with the aid of standard isodose charts, established from dose measurements in a large homogeneous phantom. The International Commission on Radiological Units and Measurements (ICRU 1963) has recommended that the measurements be made in a cubic water phantom with sides of at least 30 cm. The beam is usually directed at right angles to the plane surface of the phantom. When there are differences of radiophysical significance, between these standardized conditions and those arising in the irradiation of a patient, either the charts must be corrected or, in appropriate cases, compensation must be made for the differences. Since both the correction and compensation methods are approximate, some difference may remain between the dose distribution determined and the distribution actually obtained. Errors also occur due to limited accuracy in the determination of geometrical quantities. It therefore seems desirable that the dose in an irradiated volume should be checked by means of measurements during actual treatment. The most advantageous

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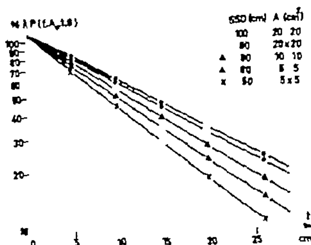



Fig. 1. Logarithm of the percentage dose along the beam axis as a function of the depth. Values taken from Brit. J. Radiol. Suppl. 10.

with a vibrating reed electrometer. In all the measurements at least 10 cm of water or mix D were located behind the chamber recording the exit dose.

## Method of calculation

*Derivation of formulas for square beams.* A coordinate system has been introduced to make it easier to define the position of a point in the beam. This system has its origin along the beam axis at a distance from the source equal to the source surface distance. The $x$ and $y$ axes are perpendicular to the beam axis and parallel to the sides of the rectangular beam. The $t$ axis coincides with the beam axis. For symmetric rectangular beams, the cross-section at a depth of 0.5 cm in the phantom is defined as

$$A_0 = 2a \times 2a \tag{1}$$

and is called field size, $(a, 0, 0.5)$ being the coordinate along the $x$ axis for the point where the dose is 50 % of that at the point $(0, 0, 0.5)$ and $(0, a, 0.5)$ being the coordinate along the $y$ axis of the point where the dose is 50 % of that at the point $(0, 0, 0.5)$.

By expressing the dose along the axis of the beam as a function of the depth with the field size as parameter, i.e. obtain straight lines in a log-linear diagram for depths greater than 5 cm. The dose at depth $t$, as a percentage of the dose at 0.5 cm, is expressed by

$$P(f, A_0, t, s) \tag{2}$$

solution is naturally to measure the dose at the points where accuracy is important such as in the tumour volume and in organs of high radiosensitivity This cannot however at present be generally achieved in practice.

Measurements with so-called Bg-chambers have been made at Radiumhemmet for a number of years on the exit side of a patient in order to estimate the dose along the axis of the beam. This radiation detector has been shown by SIEVERT (1934) SKÖLDBORN (1959) and by DAHL & VIKTERLÖF (see HULTBERG et coll 1959) to have a low energy dependence and to give good reproducibility It is the aim of this paper to elucidate the theoretical assumptions for using exit dose measurements to calculate the dose distribution in a patient.

Methods for making individual corrections to standard dose distributions by means of exit dose measurements have been previously described

KORNELSEN (1954) determined correction factors along the axis of the beam for roentgen irradiation (HVL 1 3 mm Cu) by using a 3 cm diameter ion chamber He made use of the established relationship the logarithm of the dose decreases proportionately with the depth (except near the surface) and obtained a satisfactory accuracy when using two beams in opposite positions.

WOODLEY et coll (1960) measured the exit dose for 250 kV and 2 MV roentgen rays by means of an ion chamber with a collecting electrode of 3 cm diameter The deflection of the measuring instrument was expressed as a function of the thickness of a water phantom placed in the beam The equivalent water thickness of the patient was read off on this diagram and the doses at points within the irradiated tissue volume were corrected proportionally unless knowledge of anatomical inhomogeneities permitted a discontinuous modification of the internal portion of the treatment plan

*Treatment units and measuring equipment* The measurements described below were carried out with the kilocurie cobalt 60 units at Radiumhemmet Gammatron I (HULTBERG et coll 1959) and Eldorado Super G (HULTBERG et coll 1962) These are equipped with block diaphragms, the first with its front at 31 cm and the other with its front at 35 cm from the source the source in each case being 2 cm in diameter A light beam simulating the geometry of the gamma beam is used

Except where otherwise stated the measurements were made in a water phantom (30 × 30 × 40 cm) with perspex walls by using an ion chamber (BENNER et coll 1959) with an outer diameter of 4 5 mm and a length of 15 mm This chamber in comparative studies was found to give the same results as Bg-chambers for this type of measurement The positioning of the chamber in the desired position in the phantom was simplified by using an automatic isodose recorder (LARSSON et coll 1963) The ionization current was amplified

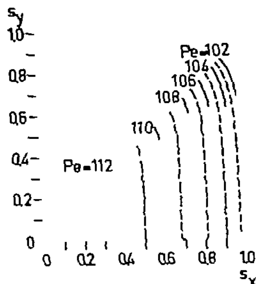



Fig. 3 The extrapolated percentage surface dose as function of the position in the field. $s_x = \frac{x}{-1}$ and $s_y = \frac{y}{-1}$ express the position in the field; and $y$ are two mutually perpendicular coordinate axes parallel with the sides of the field with their origins the centre of the field; and are the coordinates of the field limits

Even for lines parallel to the axis of the beam the logarithm of the dose decreases approximately linearly with the depth in the phantom. Measurements have shown this relationship to hold within the whole useful area of the beam. With useful area we mean the area where the dose is greater than, or equal to 90 % of the dose in the centre of the beam at a given depth. This approximately applies in an area with a cross-section of $2(a - 1) \times 2(a - 1)$ at all depths in the phantom for the two above mentioned cobalt 60 units.

$P$ (80 $A_s$, 0, $s$) for lines parallel with the beam axis was calculated by the method of least squares from previously measured two-dimensional standard isodose charts. These charts show the dose distribution in a principal plane, i. e. a plane along the beam axis and parallel with two of the sides of the rectangular field (ICRU 1963) This plane can be the $x - t$ plane. If $P$ is expressed as a function of the $x$ coordinate the curves obtained for the various field sizes are all of the same shape. It was previously shown that the value at the origin is approximately independent of the field size Since this is the case for $x = a - 1$ too we define $s$

$$s = \frac{x}{a-1} \tag{4}$$

Then all the curves nearly coincide The curve in Fig 2 was established on the basis of the values of $P$ (80 $A_s$, $0$ $s$) calculated from the standard isodose

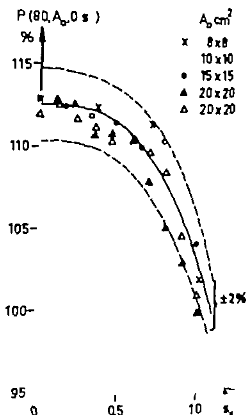



Fig 2 The extrapolated percentage surface dose as a function of the position in the equivalent standard isodose chart The continuous line obtained by the method of least squares from the standard isodose charts. The points plotted are calculated from doses measured at depths of 20 and 10 cm

were $f$ is the source surface distance

$A_0$ is the field size i e the cross-section of the beam at a depth of 0 5 cm in the phantom

$t$ is the depth in the phantom and

$s$ is a function of the distance to the beam axis this is defined in eq (5) In this case $s = 0$

The values in Fig 1 have been taken from the British Journal of Radiology Supplement No 10 (1961) When the straight lines are extrapolated to the surface they come very close to the same point The extrapolated value for $t = 0$ varies only by a small percentage for source surface distances in the range between 50 and 100 cm and for field sizes between 5 × 5 cm and 20 × 20 cm All the cases dealt with below concern the relationships with a nominal SSD of 80 cm and with field sizes between 5 × 5 cm and 20 × 20 cm The extrapolated value expressed by $P$ ($f$ $A$ 0 0) was calculated by the method of least squares giving

$$P\,(80\ A_0, 0\ 0) = 112\ 5 \pm 1 \qquad (3)$$

where $25 < A < 400$ cm²

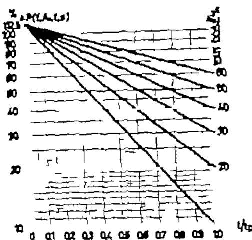


Fig 4 Diagram for determination of the percentage dose a given depth ($t$) from the exit dose (measured t depth $t_0$) The lines drawn pply to the dose along the beam axis.

The centre dose may then be calculated without knowing the values of $A$ and $t_p$. Since from the diagram in Fig 3 $P$ (80 $A_0$, 0 0) only varies between the values 102 % and 113 % eq (10) can be used within the whole of the useful area with a margin of error of $\pm$ 3 % if the constant 10 6 is replaced by 10 4 This equation is often used in pratice.

Eq (7) may also be solved graphically with the aid of a log-linear diagram. The principle is evident from Fig 4 The procedure for the determination of a dose at an arbitary depth $t$ when the exit dose at a depth $t_p$ is known is as follows: $s$ and $s$ are determined $P$ is read from the diagram in Fig 3 a straight line is drawn on a log-linear diagram between $P$ and the measured value of the exit dose $P(f\ A_0, t, s)$ is read off for the desired depth.

With the aid of the values in the depth-dose table mentioned, it was found that this method gives an error not exceeding 1 to 2 % along the beam axis up to 4 cm from the surface The error is greater nearer the surface, at $t = 2$ cm a value approximately 5 % too high is obtained. In practice, however correction with the aid of exit dose measurements of the standard dose distributions nearer the surface than 4 cm would only be of interest in exceptional cases.

An experimental investigation was performed in order to establish the magnitude of the errors introduced when this calculation method is used in practice

*Verification of the formulas for varying depths.* The doses were measured in one of the principal planes at points along $L_1$ and $L_2$ in the water phantom accord

charts The points plotted were obtained by extrapolating to the surface the lines through the dose values measured at the depths of 10 and 20 cm. It will be seen that all the points plotted for the various square fields lie within $\pm 2\%$ of the curve. The measurements for the field size $20 \times 20$ cm were made on two different occasions

The dose measurements at the depths of 10 and 20 cm were extended to the whole planes. The diagram in Fig 3 was obtained by extrapolation to the surface giving the relationship between $P$ (80 $A$ 0 $s$) and the intersection point of the line with the surface. This point is defined by the function $s$ which gives the position in the $x - y$ plane of a line parallel to the beam axis

$$s = (s_x, s_y) = \left(\frac{x}{a-1}, \frac{y}{a-1}\right) \tag{5}$$

The percentage dose along a line parallel with the beam axis may thus be expressed as follows for depths $t$ and $t_p$ respectively

$$\left.\begin{aligned} P(f, A_w, t, s) &= P(f, A_w, 0, s)\, e^{m(f, A_w)\, t} \\ P(f, A_w, t_p, s) &= P(f, A_w, 0, s)\, e^{m(f, A_w)\, t_p} \end{aligned}\right\} \tag{6}$$

where $m$ is the angular coefficient for the corresponding straight line in the log linear diagram (cf Fig 1) In the following $t_p$ is used to indicate the thickness of the irradiated object parallel to the beam axis.

By substitution

$$P(f, A_w, t, s) = [P(f, A_w, 0, s)]^{\frac{t_p - t}{t_p}}\, [P(f, A_w, t_p, s)]^{\frac{t}{t_p}} \tag{7}$$

The percentage dose at an arbitrarily chosen point ($x$ $y$ $t$) can then be calculated when the percentage dose at a depth $t_p$ is known

When the centre dose has to be calculated i e the dose midway between the entrance and exit surfaces eq (7) may be simplified to

$$P(f, A_w, t_p/2, s) = \sqrt{P(f, A_w, 0, s)\; P(f, A_w, t_p, s)} \tag{8}$$

Since $P(f, A_w, t_p, s)$ is the dose measured at the exit surface the thickness of the irradiated object need not be known for these calculations

For doses along the beam axis, additional simplifications may be made

$$P(f, A_w, t_p/2, 0) = \sqrt{P(f, A_w, 0, 0)\; P(f, A_w, t_p, 0)} \tag{9}$$

By putting $P(f, A_w, t_p/2, 0) = P_C$, which means the centre dose as a percentage of the dose at 0 5 cm

$P(f, A_w, t_p, 0) = P_f$ which means the exit dose as a percentage of the dose at 0 5 cm and

$\sqrt{P(80, A, 0, 0)} = \sqrt{112\,5} = 10\,6$ cf eq (3)

eq (9) may be simplified to

$$P_C = 10\,6 \sqrt{P_f} \tag{10}$$

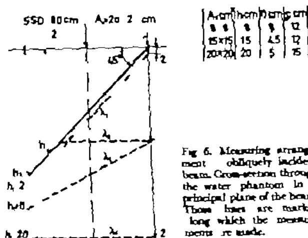



Fig 6. Measuring arrangement obliquely incident beam. Cross-section through the water phantom in principal plane of the beam. Those lines are marked along which the measurements are made.

## Calculation of dose distribution for obliquely incident beams

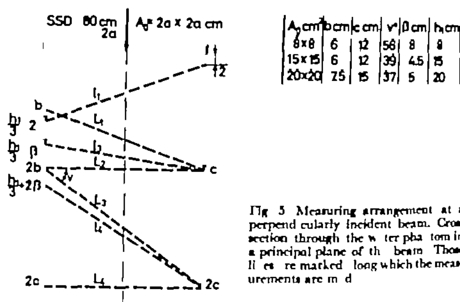
*Calculation with the aid of exit dose measurements* A correction must be made in eq (7) for obliquely incident beams. Since the intensity of the beam in air decreases approximately as the square of the distance from the radiation source, this is assumed to apply for $P\ (f\ A_0,\ 0\ s)$ as well. Thus we obtain

$$P(f\ A_m\ t\ s) = \left[\left(\frac{f}{f+k}\right)\ P_c(f\ A_0, 0\ s)\right]^{\frac{b-t}{b}}\ [P\ (f\ A_m\ t_p\ s)]^{\frac{t}{b}} \qquad (11)$$

where $k$ is the distance between the *nominal* and the actual surface measured parallel to the beam axis (cf. Fig 6)

This equation was confirmed *experimentally* for field sizes of $8 \times 8$ cm, $15 \times 15$ cm and $20 \times 20$ cm by measurements schematically shown in Fig 6. The water phantom was placed at 45° to the beam axis a further water phantom with 4 mm perspex walls was located between the nominal and the actual incident surfaces in order to determine the accuracy of the measurements. The dose was measured along the *lines* $\lambda_2$ and $\lambda$ and compared with the values at the equivalent *points along* the lines $L_2$ and $L_4$, shown in the experimental set-up in Fig 5. The maximum deviation was $\pm$ 2 %.

The wedge-shaped phantom was then removed and the dose was measured along the lines $\lambda_1$, $\lambda_2$ and $\lambda$ at the distances 1 2 3 cm perpendicular to the beam axis. Starting from the values along line $\lambda_1$, the values along $\lambda_2$ and $\lambda$ were calculated by solving eq (11) graphically (cf Fig 4). 5 % was added to the values along line $\lambda_1$ situated at a depth of 2 cm. A comparison with the directly measured values revealed a maximum error of $\pm$ 3 %. Without correction, the maximum deviation from the standard isodose charts is




| A cm | b cm | c cm | v° | β cm | h cm |
|---|---|---|---|---|---|
| 8×8 | 6 | 12 | 56 | 8 | 8 |
| 15×15 | 6 | 12 | 39 | 4.5 | 15 |
| 20×20 | 7.5 | 15 | 37 | 5 | 20 |

Fig 5 Measuring arrangement at a perpendicularly incident beam. Cross section through the water phantom in a principal plane of the beam Those lines are marked along which the measurements are made

ing to Fig 5 The distances of the points perpendicular to the beam axis were 1 2 3 cm The field sizes were 8 × 8 cm 15 × 15 cm and 20 × 20 cm respectively for the first two of the field sizes mentioned the distance ($l_2$) from the surface to the line $L_3$ varied from 12 to 24 cm and for the last field size from 15 to 30 cm Starting from the values along $L_3$ the equivalent values along $L_4$ were calculated with eq (8) The maximum deviation from the directly measured values was found to be within ± 3 %

*Verification of the formulas for beams that are not square* The dose was measured over a plane at a depth of 20 cm at 1 cm intervals for field sizes of 5 × 20 cm and 10 × 20 cm The doses at equivalent points at a depth of 10 cm were calculated with eq (8) and compared with those measured at the same points. The maximum deviation between the corresponding values was ± 2 %

It is thus evident that the dose in an irradiated water phantom may be calculated relatively simply by means of the exit dose measured under the same conditions as those existing when the standard isodose charts are obtained With this established the applicability of the method for the two conditions under which correction of the standard isodose charts will be necessary (for $^{60}$Co γ-radiation) for accurate dose planning may now be discussed Those conditions occur when the beam strikes a body contour obliquely and when the beam passes through an air filled lung

| $A_r$ cm | h cm | [illegible] cm | c cm |
|---|---|---|---|
| 8 × 8 | [illegible] | [illegible] | 12 |
| 15×15 | 15 | 4.5 | 12 |
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Fig. 6. Measuring arrangement obliquely incident beam. Cross-section through the water phantom in principal plane of the beam. Those lines are marked along which the measurements are made.

## Calculation of dose distribution for obliquely incident beams

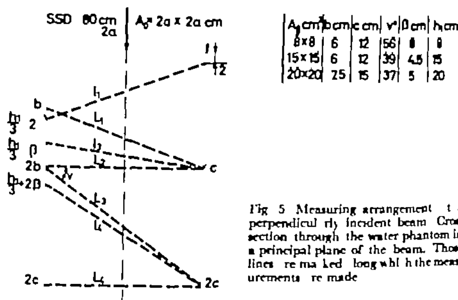
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$$P(f\ A_w, t, s) = \left[\left(\frac{f}{f+h}\right) P(f\ A_w, 0\ s)\right]^{\frac{t_p - t}{t_p}} \left[P(f\ A_w, t_p, s)\right]^{\frac{t}{t_p}} \qquad (11)$$

where $h$ is the distance between the *nominal* and the actual surface measured parallel to the beam axis (cf. Fig 6)

This equation was confirmed experimentally for field sizes of $8 \times 8$ cm, $15 \times 15$ cm and $20 \times 20$ cm, by measurements schematically shown in Fig 6. The water phantom was placed at 45 to the beam axis a further water phantom with 4 mm perspex walls was located between the nominal and the actual incident surfaces in order to determine the accuracy of the measurements. The dose was measured along the lines $\lambda_s$ and $\lambda$ and compared with the values at the equivalent points along the lines $L_s$ and $L_t$, shown in the experimental set-up in Fig. 5. The maximum deviation was $\pm$ 2 %

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| $A_0$ cm² | b cm | c cm | v° | β cm | h cm |
|---|---|---|---|---|---|
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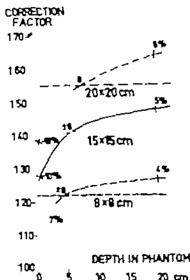



Fig. 8. Comparison between two methods for correcting standard isodose charts for obliquely incident beams. The correction factor as function of the depth in water phantom placed as in fig 6, with the field size as parameter. The straight lines are obtained by the 5.5 % per centimetre method and the curved lines by the TAR method. The inserted figures represent the differences between values given by the two methods as percentage of the TAR method.

The latter method is easier to use because no interpolation for the variation of the beam size with depth is required. Eq. (13) was checked experimentally by measuring the dose along the lines $\lambda$, $\lambda_a$, and $\lambda$ with the experimental set-up shown in Fig. 6. The values obtained with the wedge phantom in the beam were multiplied by $k_w$ defined according to eq. (13). All the values measured without the wedge phantom were within $\pm 3$ % of those calculated for the used field sizes 8 × 8 cm, 15 × 15 cm, and 20 × 20 cm. As was pointed out previously the maximum deviation from the standard isodose charts is + 140

This method is rather laborious for the correction of charts in manual dose planning. Three other methods have been given in the literature and these might be called (1) the effective attenuation coefficient method, (2) the effective SSD method, and (3) the isodose curve shift method. These have been described by ICRU (1963) and compared for accuracy by GARRETT & JONES (1962) and by DUTREIX & DUTREIX (1962); references to the original work on the different methods were included.

The effective attenuation coefficient method is from here on replaced by increasing the dose by 5.5 % per cm 'missing' tissue in accordance with JOHNS (1961). Thus $k$ and $l$ are determined as in the exit dose method, i. e. the distances are measured parallel with the beam axis. Using the isodose curve shift method, the curves are displaced parallel with the beam axis ? $k$.

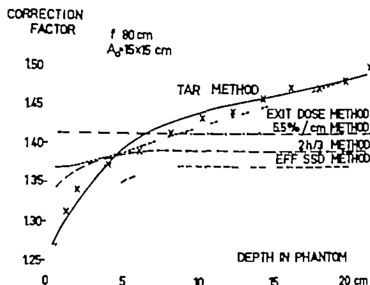



Fig 7 Comparison between various methods for correcting standard isodose charts for obliquely incident beams The correction factor as a function of the depth in a water phantom placed as in fig 6 The crosses indicate the values measured

+ 140 % The values corresponding to these charts were obtained by measuring the dose with the wedge phantom in the beam

*Comparison with other methods of calculation* A method of correcting the standard isodose charts for obliquely incident beams has been described by Du Sault & Legaré (1963) This involves multiplying the dose in the charts by the factor

$$k = \frac{T(A\ t)}{T(A\ t+h)} \tag{12}$$

where $A$ is the beam size at the depth $t + h$ cm,

$t$ is the depth in the phantom along a line from the radiation source to the point considered

$h$ is the distance between the nominal and the actual surfaces along the same line (in this case *not* parallel with the beam axis) and

$T(A\ t)$ are tissue air ratios (TAR) in accordance with Clinical Dosimetry (ICRU 1963)

Independent of this investigation it was observed (Sundbom 1964) that when using compensating filters greater accuracy was achieved by applying TAR for the beam size at a depth of 0 5 cm instead of TAR for the beam size at the actual depth i e

$$k = \frac{T(A\ t)}{T(A\ t+h)} \tag{13}$$

with the exception of the points along the line 1 (and the corresponding line l, in Fig 5) from the right hand limit of the field half way to the beam axis. The maximum deviations for the various field sizes were + 5 %, +12% and + 15 % respectively These values should be compared with the maximum deviation of + 140 % that occurs when no correction is made

### Calculation of dose distribution for beam passing through air-filled lung

The exit dose method was found to be applicable even for calculation of the dose in the irradiation of lung tissue. The assumption that this should be the case is based on the investigations carried out by BURLIN (1957) This author reported that correction methods, based on absorption differences only lead to an excessive correction factor but that corrections based on exit dose measurements produce relatively accurate correction factors. A number of experiments were made to determine the magnitude of the difference between the calculated and the measured doses. These included measurements with Bg chambers.

The experimental set up is depicted in Fig 9 This shows a cross-section of the used masonite phantom (30 × 30 × 24 cm) The Bg-chambers were introduced into sheets of perspex 5 mm thick. A varying number of masonite sheets, at depths between 3 cm and 21 cm, were replaced with sawdust with a density of 0.25 g/cm This is the same sawdust that was stated by DAHL & VIKTERLÖF (1960) to be radiation-equivalent to an air filled lung The replacement, 3 cm at a time, was made both from right to left, and vice versa, as well as from the central perspex sheet and outwards. The field sizes were 7.5 × 7.5 cm and 15 × 15 cm. The measured values of the exit dose were put into eq (8) giving the doses in the central plane of the phantom The corresponding values of the dose measured in this plane at the same time varied between 107 % and 90 of that calculated. The 90 value (i e. a dose 10 % too low) was obtained when 9 cm of sawdust was placed in front of the central perspex sheet with only masonite behind the perspex. This result was expected and is due to the 'build up of the scattered radiation (BURLIN 1957)

The same exposure to two opposed beams (with a varying sawdust-masonite distribution as above) gave a measured dose varying between 102 % and 95 % of that calculated. The 95 % value (i e a dose 5 % too low) was obtained when all the masonite was replaced by sawdust.

The equivalent measurements and calculations were made with the same experimental set-up but with the chamber holder moved from the centre of the phantom to depths of 6 and 18 cm, respectively The same degree of deviation was obtained between the measured and the calculated doses in these cases

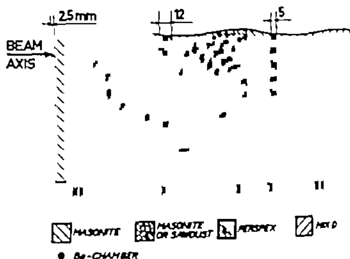



Fig 9 Cross-section through masonite phantom The masonite sheets (30 × 30 cm) can be replaced by sawdust (0.25 g/cm³) between 30 mm and 210 mm The black dots indicate Bg-chambers these are inserted into perspex sheets Mix D is placed behind the phantom

The correction factor along the axis of the beam obtained by five correction methods is shown in Fig 7 for a field size of 15 × 15 cm as a function of the depth in the phantom The phantom was placed as shown in Fig 6. When using the exit dose method of correction $t_p$ (the thickness of the irradiated object) was put equal to 20 cm Comparison with the measured values indicates that all the methods except the TAR and the exit dose methods, give too low a correction factor at large depths this is especially true for the effective SSD method Near the surface of the phantom all the methods except the TAR method and the effective SSD method give correction factors that are too high The variation of the correction factors with field size and depth in the phantom is illustrated in Fig 8 according to the TAR method and the 5.5 % per centimetre method The latter method thus gives quite high accuracy in spite of its simplicity

A comparison between methods (1) (2) and (3) was made at various points within the beam in a series of measurements. This showed the isodose curve shift method to give results quite as accurate as the others. This method has the advantage of being simple to apply to individual irradiation planning The accuracy was investigated with the aid of dose measurements with the experimental set up in Figs 5 and 6 for field sizes 8 × 8 cm 15 × 15 cm and 20 × 20 cm The lines $\lambda$ $\lambda$ and $\lambda$ were projected in the phantom placed as for measurement of standard isodose charts This gave the lines l $l_1$ and l in Fig 5 A comparison of the doses at equivalent points on equivalent lines revealed the following maximum deviations

for field size 8 × 8 cm ± 2 %
» » » » 15 × 15 cm ± 5 %
» » » 20 × 20 cm ± 6 %

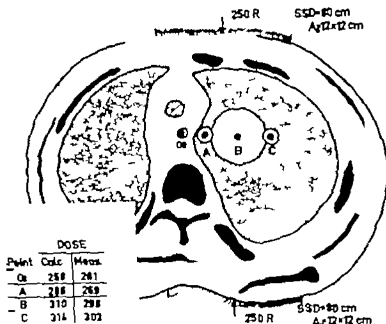



Fig 11 Cross-section through an anatomical thorax phantom containing mix D cylinder (5 cm in diameter) The positions of the beams are shown. The doses at points A, B, and C and in the oesophagus (Oe) were calculated with the aid of exit dose measurements and measured directly Dose in rad.

was placed in the lung volume Two different experimental arrangements were used as shown in Figs 10 and 11 The cross-sections in the figures are representative for the whole volume struck by the beams. The measurements were made with Bg-chambers

Irradiation with two opposed beams gave the values shown in the figures. The quotients of the measured values and values calculated from exit dose measurements at the relevant points are between 94 % and 102 % With no correction of the standard isodose charts, quotients of between 99 and 121 % were obtained

## Discussion

It is essential that regard should be paid to the material beside and behind the measuring chamber if the exit dose is to be used clinically for the calculation of the dose distribution. The formulas which have been derived above are valid, within the given margins of error only if the scattered radiation corre

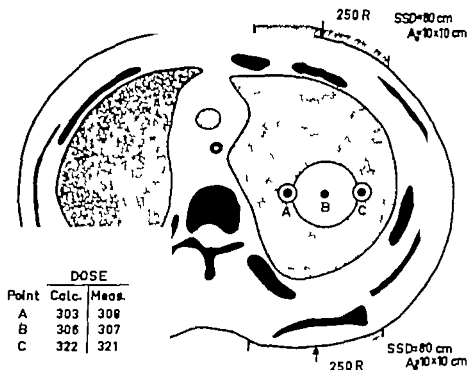



Fig 10 Cross-section through an anatomical thorax phantom containing a mix D cylinder (5 cm in diameter) The positions of the beams are shown The doses at points A B, and C were calculated with the aid of exit dose measurements and measured directly Dose in rad

A simple method of correcting for an air filled lung at the dose planning was tested This consists in increasing the dose given by a standard isodose chart by 3 % for each centimetre of lung through which the beam passes The dose was calculated in this way for both the above experiments, both within the phantom and at the exit surface In no case did the calculated dose deviate more than ± 10 % from the measured dose This degree of accuracy is obtained if the density of the air filled lung is 0 25 g/cm³ within the whole beam and if the geometric dimensions are known The dose was increased to a maximum of 160 % at the exit plane and 140 % in the planes inside the phantom.

## Calculation of dose distribution in an anatomical thorax phantom

The method of calculation of the dose distribution with the aid of exit dose measurements was tested by the irradiation of an anatomical thorax phantom The phantom is formed by a skeleton and mix D with an air filled lung represented by sawdust with a density of 0 25 g/cm (DAHL & VIKTERLÖF 1960) A mix D cylinder with a diameter of 5 cm and with channels for Bg-chambers

## RÉSUMÉ

L'auteur décrit et étudie une méthode de calcul de la dose dans les trois dimensions sur un malade, à partir des mesures des doses de sortie. Il a étudié particulièrement les cas où le rayonnement tombe à l'oblique sur le corps et où il traverse le poumon rempli d'air. L'écart entre la dose mesurée et la dose calculée était de ± 3 % dans le premier cas, et ± 10 % dans le second cas.

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sponds to that existing in a large phantom. When a patient is exposed to radiation some material must either be placed behind and beside the exit-dose measuring-chamber so as to provide this scattered radiation, or a correction must be made for the reduced scatter. The order of magnitude of this correction, when measuring with Bg-chambers, was investigated. The beam was directed at right angles to sheets of mix D with thicknesses of 10, 20 and 30 cm, respectively, in three different measuring arrangements. A 0.5 cm thick perspex sheet was placed behind mix D, the *Bg-chambers lying in this perspex sheet*. Irradiations were made with field sizes of 7.5 × 7.5 cm and 15 × 15 cm (SSD 80 cm), with air and mix D, respectively, behind the chambers. This resulted in a voltage drop between 95 % and 90 % with air as compared with mix D placed behind the chambers for the same dose at a depth of 0.5 cm within the phantom.

For irradiation of the thorax in individual patients, calculation of the dose distribution is difficult. This is largely due to the problem of establishing the variations in density in the volume to be irradiated. An accurate correction will depend upon the dimensions of the lungs and on knowledge of how radiation is absorbed and scattered in the various parts of the lungs.

*With three-dimensional dose calculations based on exit dose measurements*, the degree of accuracy stated above is obtained without these relationships being known. This method has the additional advantage that correction for bone tissue, for oblique incidence and for different beam sizes may be made at the same time. When calculating the dose in the central plane, the accuracy is independent of error in measurements of the patient thickness.

## SUMMARY

A method of calculating the dose in three dimensions in a patient with the aid of exit dose measurements is described and discussed. Particular attention is paid to the conditions when the beam strikes the body obliquely and when it passes through an air filled lung, the deviation between the measured and calculated doses being within ± 3 and ± 10 %, respectively.

## ZUSAMMENFASSUNG

Eine Methode zur Bestimmung der Dosisverteilung in drei Dimensionen mit Hilfe der Messung der Austrittsdosis wird beschrieben und erörtert. Besondere Aufmerksamkeit wird den Bedingungen gewidmet, wenn das Strahlenbündel schräg den Körper trifft und wenn es durch eine luftgefüllte Lunge passiert. Die Abweichung zwischen den gemessenen und errechneten Werten liegt innerhalb ± 3 % beziehungsweise innerhalb ± 10 %.

work. By representing the effect of the different absorbers with 'subtractive isodose charts' according to the method described below only one measurement needs to be performed with each absorber in an optional beam at each source-surface distance.

*Principle of the method.* In order to describe the simple principle on which this method is based all the rays which reach the patient are assumed to come directly from the radiation source. A shielding filter (absorber) inserted into any beam, would on this assumption modify the radiation intensity over the cross-section of the beam in a way depending only on the effective attenuation of the filter. This, in turn, would of course have for effect that the dose rate at an arbitrary point within the irradiated object is reduced by a value which is independent of the size and shape of the beam. Consequently the reduction in dose rate in a given plane can be represented by a 'subtractive isodose chart'. This negative isodose chart standardized in a suitable way can on dose planning be added to the standard isodose chart for the particular beam chosen, by means of which the dose distribution with shielding filter inserted may be obtained.

However not all the radiation that reaches the patient comes directly from the source; about 12 % constitutes scatter-radiation from the head of the treatment unit (CORMACK & JOHNS 1958). This means that the field size and the position of the shielding filter in the beam may influence the effect of the filter and consequently the subtractive isodose chart. Measurements have been made in order to establish the magnitude of error in the practical use of such standardized subtractive isodose charts. The measurements are reported below.

## Testing of the method

The Eldorado Super G unit at Radiumhemmet (HULTBERG et coll. 1962) was used. This unit is provided with a block diaphragm, the front of which is situated 35 cm from the source; the source has a diameter of 2 cm.

The dose measurements were performed in a water-filled perspex container (30 × 30 × 40 cm) with an ionization chamber (BENNER et coll. 1959) having an external diameter of 4.5 mm and a length of 15 mm. The ionization current was amplified by a vibrating reed electrometer. The wave length dependence of the chamber is within ± 10 % at radiation qualities corresponding to the interval between HVL 0.1 mm Cu (100 kV, 1 mm Al) and HVL 14.7 mm Cu (cobalt 60). The chamber is connected with an automatic isodose recorder (LARSSON et coll. 1963).

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# METHOD OF DOSE PLANNING ON APPLICATION OF SHIELDING FILTERS IN COBALT 60 TELETHERAPY

by

LENNART SUNDBOM

It is often desirable in radiotherapy to protect tissue enclosed within a volume which is to be given a high dose The reason may be that the tissue has previously been heavily irradiated or that it is very radiosensitive Protection against irradiation of tissues can be achieved by inserting absorbers in suitable places in the beam.

A method of protection has been described by TRANTER (1959) and TAYLOR (1963) who used it in the supplementary radiation treatment of the parametria in cases in which the vagina and uterus had already been irradiated by radium sources. LEDERMAN (1957) has reported on the protection of the lense of the eye in the radiation treatment of orbital tumours Application of shielding filters in moving beam therapy has been described by TAKAHASHI et coll (1961) and by PROIMOS (1963)

It is of course theoretically possible to work out isodose charts for different combinations of source surface distances, field sizes, absorbers and their position in the beam but this in practice would involve an excessive amount of

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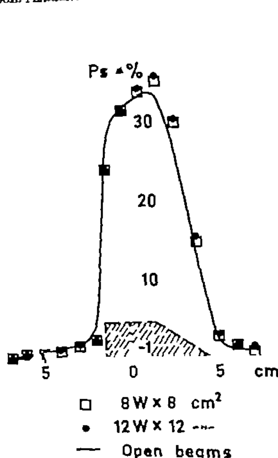



Fig 2 Differences in dose rate with and without the shielding filter in the beam, depth of 10 cm in the phantom, as function of the distance to the beam axis. The cross section of the filter is projected to this depth.

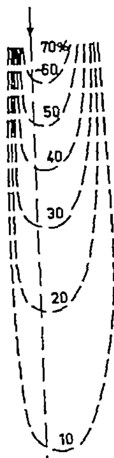



Fig 3. Subtractive isodose chart for the shielding filter standardized to the dose in beam with field size 12 × 12 cm at depth of 0.5 cm in the phantom.

Measurements and calculations were made in a corresponding way using a field size of 12 × 12 cm, with the filter displaced 1.5 cm in the principal plane in both directions relative to the position in the above mentioned experimental set up Because of the divergence of the gamma rays, this is equivalent to a displacement of ± 2.25 cm at a depth of 10 cm in the phantom. With the filter at the origin of the diagram, the calculated values of the dose rate reduction are within ± 2 % of the curve in Fig 2

If a shielding filter is to be used in a beam with wedge filter it may be

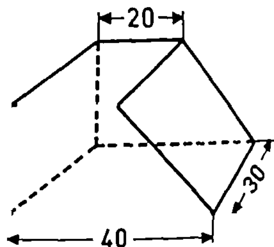



Fig 1 The d mensions ( n mm) of the shieldi g filter used in the investigation

A shielding filter of lead suited to the purpose was prepared the shape and dimensions of which are shown in Fig 1 It was placed on a perspex sheet, 5 mm thick, at a distance of 60 cm from the source with its plane of symmetry in the principal plane of the beam The latter is defined as the plane containing the beam axis and being parallel to two of the sides of the rectangular fields The source surface distance was constantly 80 cm

The dose measurements were for practical reasons limited to a few points in the phantom These points were chosen so as to be situated in the principal plane both along the beam axis, at depths of 2 cm and 20 cm and along a line perpendicular to the beam axis at a depth of 10 cm. The dose was measured along the latter line at intervals of 1 cm within $\pm$ 10 cm from the beam axis.

The dose rates were measured at the different points, with field sizes of 8×8 cm 12×12 cm 16×16 cm and 20×20 cm with and without the shielding filter in the beam The filter was placed as shown in Fig 2 The diagram origin in this set up coincides with the beam axis. The cross section of the filter drawn in the figure has been projected to the depth of 10 cm. By subtracting one from the other of the two values obtained at one point a measure of the decrease in the dose rate with the use of a shielding filter will be obtained

It was found that the decrease at each one of the measurement points varied within $\pm$ 2 % for the different field sizes used and consequently that the filter reduces the dose rate almost independently of the field size used The curve in Fig 2 was established by using the mean value of the reduction in dose rate obtained at the different points along the line at a depth of 10 cm. This curve shows the reduction in dose rate in percentage of the dose rate at a depth of 0 5 cm with a field size of 12 × 12 cm as a function of the distance to the beam axis

## RÉSUMÉ

Pour protéger les tissus en radiothérapie à dose élevée, on peut utiliser des absorbeurs (filtres de protection) placés dans le faisceau dans une position convenable. On peut déterminer leur influence sur la distribution de dose grâce à des cartes d'isodoses soustractives. Ceci permet d'établir simplement le plan d'irradiation pour des filtres de protection placés arbitrairement dans divers faisceaux. La précision obtenue est satisfaisante.


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necessary to establish a separate subtractive isodose chart because the radiation is attenuated by the thickness of a filter according to an exponential *function* whereas the subtractive isodose chart is established by subtraction. In order to illustrate this measurements corresponding to the above mentioned experiments were performed using beams with wedge filter and field sizes of 8 × 8 cm and 12 × 12 cm Thus the dose rates measured in the beam without shielding filter were subtracted from the corresponding values obtained with filter in the beam. The resulting values were multiplied by the quotient of the dose rates at a given point determined by the position of the shielding filter without and with wedge filter in the beam This point corresponds to the origin in Fig 2 The differences in the calculated values at the different points and with different field sizes and varied positions of the shielding filter are within ± 2 %

The calculated values along the line at the depth of 10 cm are shown in the diagram (Fig 2) from which will be seen that they do not coincide with the curve established for open beams The difference for the highest value (at the point 2 cm to the right) is 6 %

It may thus be concluded that one isodose chart can be used for open beams independently of field size but that it may be necessary to establish separate charts for beams with and without wedge filter

The subtractive isodose chart for the shielding filter when placed in an open beam is given in Fig 3 This chart was drawn by graphical subtraction of the isodose curves measured for an open beam field size 12 × 12 cm from the curves with filter in the same beam

## SUMMARY

It is sometimes desirable in radiotherapy to protect tissue enclosed within a volume which is to be given a high dose The protection can be achieved by inserting absorbers (shielding filters) in suitable positions in the beam. The influence of these filters on the dose distribution may be described with subtractive isodose charts which will facilitate dose planning with shielding filters arbitrarily placed in different beams. The accuracy obtained is satisfactory

## ZUSAMMENFASSUNG

In Radiotherapie ist es manchmal wünschenswert, Gewebe innerhalb eines Volumens zu schützen, das einer grossen Strahlendosis ausgesetzt werden soll. Dies kann durch Anbringen von Abschirmungsfiltern im Strahlenbündel erreicht werden Der Einfluss dieses Filters auf die Strahlendosisverteilung kann mit subtraktiven Isodosendiagrammen illustriert werden, was die Planierung der Strahlendosisverteilung bei der Verwendung von Filtern in verschiedenen Strahlenbündeln erleichtert.

RUBANOVSKAIA & USHAKOVA (1957) observed no effects after the repeated administration of magnesium sulphate, and according to TAYLOR et coll. (1962) the absorption of $^{85}$Sr from the intestine was not diminished by the administration of sulphate ions.

In view of these contradictory results, the effectiveness of various sulphates on the absorption of $^{85}$Sr from the digestive tract of rats was compared under the same experimental conditions. It was borne in mind that although strontium may be bound to barium sulphate mainly by adsorption, it forms the insoluble strontium sulphate with sodium or magnesium sulphates. Whilst barium sulphate is not absorbed from the intestine and passes unchanged, soluble sulphates are partly absorbed and act in the intestine as salinic cathartics.

Combinations of various sulphates were tested in these experiments, considering and also the possibility of increasing the effect of the sulphates as well as of hastening the movement of the intestinal contents, and thus also of the sulphates with bound radiostrontium.

## Methods

*Experimental animals* In all, 272 male Wistar albino rats, weighing 165 to 205 g, were used. In each experiment, animals with the smallest possible difference in weight (generally 10 to 20 g) were employed. The rats were kept in metabolic glass cages (VOLF 1958) and were given a standard Larsen diet and drinking water ad lib. Food and water were removed before the beginning of the experiment (at 20 and 12 hours respectively) and replaced in the cages two hours later. Radiostrontium and sulphates were given by a stomach tube under light ether anaesthesia. Care was taken to administer equal quantities of liquid to each animal. The rats were sacrificed 48 hours after the administration of radiostrontium.

*Radioactive $^{85}$Sr* chloride was supplied by the Nuclear Science and Engineering Corporation of Pittsburgh, U.S.A. diluted in 0.5 N of hydrochloric acid radiochemical purity 99 %, total content of 0.1 mg of solids in 0.77 mCi. This stock solution was diluted with distilled water and adjusted to a pH of 6 to 7 with sodium hydrogen carbonate. Each animal was given 1 to 2 $\mu$Ci $^{85}$*Sr in 0.1 ml.*

*Tested substances* The calcium, strontium and barium sulphates were prepared in the laboratory and the sodium and magnesium sulphates were obtained from Lachema, CSSR. Sklabaryum (Slovakofarma, CSSR) consists of barium sulphate (86.8 %) talc (10.0 %) bentonite (3.0 %) sodium citrate (0.2 %) and correctives. The preparations were of equimolar strength in all the

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# RETENTION OF $^{85}$Sr IN RATS

## I Effect of sodium, magnesium, calcium strontium and barium sulphates

*by*

VLADIMÍR VOLF and ZDENEK ROTH

Barium sulphate has been found to diminish the absorption of radiostrontium from the gastrointestinal tract (BALABUCHA 1959 CATSCH 1956 SEMEKOV 1953) and to increase the excretion of absorbed radiostrontium in the faeces in rats (VOLF 1959 1960) A preparation of barium sulphate was used as first aid treatment after the accidental inhalation of $^{85}$Sr in man and its effectiveness was verified in rats under similar conditions (VOLF 1961) The effect of this preparation on the intestinal absorption and excretion of radiostrontium was also followed up in a clinical study of several cases of carcinoma (VOLF 1963)

MACDONALD et coll (1952 1955) described a similar influence of sodium and magnesium sulphates on the absorption of radiostrontium from the intestine On the other hand COPP & GREENBERG (1944) reported no substantial decrease in the absorption after the administration of magnesium sulphate and JONES (1955) doubted the effectiveness of sodium and calcium sulphates.

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Table 1

*Effect of Skiabaryum and various sulphates administered orally in doses of 0 8 mM immediately or 10 min after oral contamination with $^{85}Sr$*

| Substances tested | Time of administration | Number of animals | Percentage of $^{85}Sr$ administered: Whole body, After 24 hours, $\bar{x} \pm s_{\bar{x}}$ | Percentage of control | Whole body, After 48 hours, $\bar{x} \pm s_{\bar{x}}$ | Percentage of control | Skeleton, After 48 hours, $\bar{x} \pm s_{\bar{x}}$ | Percentage of control |
|---|---|---|---|---|---|---|---|---|
| Controls | Immediately after $^{85}Sr$ | 18 | 28.8 ± 6.1 | 100 | 20.6 ± 4 8 | 100 | 19 0 ± 4.5 | 100 |
| $Na_2SO_4$ | | 6 | 20.1 ± 3.2 | n.s. | 12.8 ± 1 7 | a. | 10.4 ± 2.5 | 55 |
| $MgSO_4$ | | 6 | 25.1 ± 14.3 | n.s. | 13.9 ± 4.5 | n.s. | 12.7 ± 3.5 | n.s. |
| $CaSO_4$ | | 6 | 35.3 ± 14 2 | n.s. | 15.7 ± 10 4 | a. | 10.5 ± 1.8 | 55 |
| $SrSO_4$ | | 6 | 22.0 ± 17.3 | | 16.4 ± 10.4 | | 12.8 ± 11 4 | n.s. |
| $BaSO_4$ | | 6 | 22.5 ± 10.4 | n.s. | 8.5 ± 5.5 | 41 | 4.9 ± 3.3 | 26 |
| Skiabaryum | | 6 | 22.0 ± 16.2 | | 12.9 ± 7.2 | n.s. | 11 0 ± 5 7 | 58 |
| Controls | 10 min after $^{85}Sr$ | 12 | 48.3 ± 9 4 | 100 | 35.0 ± 6.7 | 100 | 32.4 ± 6 7 | 100 |
| $Na_2SO_4$ | | 5 | 31.2 ± 23.4 | 65 | 25.0 ± 16.8 | 71 | 20 4 ± 12.9 | 63 |
| $MgSO_4$ | | 6 | 52.9 ± 15.6 | n.s. | 22 6 ± 5 6 | 64 | 18 6 ± 3.5 | 57 |
| $CaSO_4$ | | 6 | 25 4 ± 6 8 | 44 | 14.2 ± 5.7 | 40 | 12.6 ± 7.9 | 39 |
| $SrSO_4$ | | 6 | 45 4 ± 19 1 | n.s. | 25.5 ± 8.4 | 73 | 21 9 ± 7.8 | 68 |
| $BaSO_4$ | | 6 | 32.4 ± 9.5 | 67 | 19.4 ± 9.2 | 55 | 14 7 ± 1 7 | 45 |
| Skiabaryum | | 6 | 31.5 ± 13.2 | 65 | 22.1 ± 8.4 | 63 | 18.9 ± 7 1 | 58 |
| Controls | 10 min after $^{85}Sr$ | 12 | 55.1 ± 15.6 | 100 | 35.8 ± 6 8 | 100 | 24.2 ± 4.5 | 100 |
| $Na_2SO_4$ | | 6 | 29.5 ± 10.5 | 53 | 16.1 ± 6.3 | 45 | 11 7 ± 5.0 | 48 |
| $MgSO_4$ | | 6 | 31 4 ± 10.3 | 57 | 16.0 ± 4.0 | 45 | 9.9 ± 2.9 | 41 |
| $CaSO_4$ | | 6 | 41 4 ± 21.3 | n.s. | 16.0 ± 5.0 | 45 | 10.8 ± 3 1 | 45 |
| $SrSO_4$ | | 6 | 36.1 ± 10 2 | 66 | 25.4 ± 7 1 | 71 | 18.5 ± 4.7 | 76 |
| $BaSO_4$ | | 5 | 34.9 ± 27.3 | 53 | 10.6 ± 6 6 | 30 | 7 4 ± 4.6 | 31 |
| Skiabaryum | | 6 | 46.5 ± 19 5 | n.s. | 16.9 ± 5.3 | 45 | 11.0 ± 4 0 | 45 |

Content of $^{85}Sr$ in 1 femur times 20

Arithmetic mean ± standard error of the mean multiplied by t-value for 95 % confidence level

The difference is not statistically significant

## Results

Data from three experiments designed to study the effect of equimolar amounts of Skiabaryum and various sulphates upon the intestinal absorption of $^{85}Sr$ are collected in Table 1 The average whole body retention 24 hours after $^{85}Sr$ administration in the treated animals was between 30 and 50% lower as compared with the controls, although this could not always be proved

experiments. The sulphates were administered orally 0.8 mM in 2 ml of distilled $H_2O$ per dose in the first experiment immediately after oral contamination with $^{85}Sr$, in the other experiments 10 min later. Each dose of Skiabaryum also had to contain 0.8 mM of barium sulphate.

*Measurements.* The whole body activity of the rats was determined with the scintillation equipment of the institute. A NaI crystal (Tl) 45 × 25 mm (later 45 × 50 mm) in connection with a photomultiplier was used for detection.

The animals were placed in round aluminium boxes (100 mm in diameter covered by perforated 3 mm plastic material) and these were put in a lead shielding under the center of the crystal at a distance of 15 cm. The counting efficiency of the equipment was 0.5 to 1%, which is satisfactory for whole body counting with doses of $^{85}Sr$ administered in short term experiments. Counting of the whole body activity in the rats was started 15 min after the administration of $^{85}Sr$ and repeated after 24 and 48 hours.

The dissected femur was placed in a test tube, dissolved in 1 ml concentrated nitric acid and scintillation counting was performed with a well type NaI crystal (Tl). The counting efficacy was between 30 and 40%, sufficient counts being taken to keep the statistical counting error within 2%.

## *Evaluation of results*

All values are expressed as a percentage of the administered dose. For the total retention of $^{85}Sr$ the number of counts per minute obtained with each rat during the initial whole-body measurement was considered to be 100%. For the $^{85}Sr$ retained in the bones, 100% of the administered dose was determined by means of standards prepared by injecting one $^{85}Sr$ dose into a known volume of carrier strontium solution. The amount of $^{85}Sr$ retained in the whole skeleton was calculated by multiplying the percentage of the $^{85}Sr$ dose detected in one femur by an empirical factor of twenty.

The arithmetic means as well as their 95% confidence level were calculated (standard errors of the means multiplied by the corresponding t values were added to and subtracted from the arithmetic means). The average values were compared with the help of Duncan's test (DUNCAN 1957) of simultaneous evaluation of many averages, modified to various variances of each group compared. Where the average of the experimental values differed significantly from the control values, the effectiveness of various factors in influencing the metabolism of $^{85}Sr$ was calculated and expressed in the form of a percentage of the control values.

The appendix gives detailed information regarding the methods of statistical evaluation.

of strontium sulphate which in one of the experiments was considerably less effective. It reduced the retention of $^{90}$Sr by 29 / at the utmost, this being the lowest effect observed. After barium sulphate, on the other hand, there was always a marked decrease 70 % was the highest observed efficacy Yet, regarding the average effect, the barium sulphate group did not show any substantial difference from the other experimental groups.

There was a significant decrease in the skeletal content of $^{90}$Sr after the administration of sulphates and Skiabaryum, usually by 40 to 60 / There was no marked difference in the average effect of the sulphates tested or of Skia baryum, with the exception of strontium sulphate which decreased the average retention of $^{90}$Sr by a maximum of 32 / in comparison with the controls. This represents the lowest effect observed. In one case it was impossible to prove any great decrease in the retention of $^{90}$Sr even after magnesium sulphate. Barium sulphate, however lowered the average skeletal retention by as much as 74 % which is the highest effectiveness observed although the average effect of barium sulphate could not even here be statistically distinguished from the effect of other agents.

The effect of the substances tested, and administered immediately after oral contamination with $^{90}$Sr seems to differ only slightly from the effect of the same substances when given 10 min later

Data from two experiments, in which a comparison was made of the action of sulphates when administered alone and in combination, are given in Table 2 This table also shows the results of another experiment in which a combination of Skiabaryum with sodium sulphate was tested.

When adding sodium or magnesium sulphate to calcium sulphate, the effect on $^{90}$Sr retention improved only slightly especially as compared with sodium sulphate alone (roughly by 30 %)

A significantly greater effect than with sulphates alone was produced by a combination of barium sulphate with sodium or magnesium sulphate. The average retention of $^{90}$Sr after 48 hours in comparison with the controls and with sodium sulphate decreased by about 80 These combinations were also more effective by about 70 to 80 % as compared with magnesium sulphate by 50 to 60 compared with calcium sulphate, and by 30 to 50 / when compared with barium sulphate There was always a more marked decrease in the retention of $^{90}$Sr in the skeleton than in the whole organism.

The combination of barium and sodium sulphates was significantly more effective than a similar combination of Skiabaryum with sodium sulphate. The whole body retained 45 % less and the skeleton 35 % less $^{90}$Sr after the administration of barium and sodium sulphates than after Skiabaryum. The difference is statistically significant.

**Table 2**

*Effect of various sulphates and their combinations administered orally in doses of 0 8 mM 10 min after oral contamination with Sr*

| Substances tested | Number of animals | Percentag of ⁸⁵Sr administered: Whole body, After 24 hours, $\bar{x} \pm ts_{\bar{x}}$ | Percentage of control | Whole body, After 48 hours, $\bar{x} \pm ts_{\bar{x}}$ | Percentage of control | Skeleton, After 48 hours, $\bar{x} \pm ts_{\bar{x}}$ | Percentage of control |
|---|---|---|---|---|---|---|---|
| $Na_2SO$ | 10 | 43 6 ± 11.3 | 100 | 30 0 ± 6.3 | 100 | 22.4 ± 4 7 | 100 |
| $MgSO$ | 10 | 33 1 ± 8.5 | n.s. | 22 0 ± 3 9 | 73 | 17.8 ± 3.6 | n.s. |
| $CaSO$ | 5 | 33.8 ± 10 6 | n.s. | 22.2 ± 7.5 | n.s. | 18.0 ± 5.9 | n.s. |
| $BaSO$ | 5 | 54 4 ± 34.2 | n.s. | 11.5 ± 8.2 | 38 | 8.2 ± 4 0 | 36 |
| $CaSO$ + $Na_2SO$ | 5 | 28.2 ± 14 3 | n.s. | 16.3 ± 4 6 | 54 | 14 8 ± 5 3 | 66 |
| $CaSO$ + $MgSO$ | 6 | 44 0 ± 24.9 | n.s. | 21.9 ± 9 7 | n.s. | 16 1 ± 4.3 | 72 |
| $BaSO$ + $Na_2SO$ | 5 | 22.7 ± 11.8 | 52 | 5 7 ± 2 3 | 19 | 3 7 ± 1 6 | 16 |
| $BaSO$ + $MgSO$ | 6 | 21 6 ± 7 6 | 50 | 6.7 ± 3 0 | 22 | 4 4 ± 2 0 | 19 |
| Controls | 12 | 33 7 ± 9 0 | 100 | 24 9 ± 7 7 | 100 | 2? 4 ± 6.8 | 100 |
| $CaSO$ | 6 | 24 3 ± 8 7 | n.s. | 18.2 ± 6 7 | n.s. | 15.8 ± 6.4 | n.s. |
| $BaSO$ | 6 | 19 7 ± 6 8 | 58 | 12 0 ± 3 0 | 48 | 10 6 ± 3.1 | 47 |
| $CaSO$ + $Na_2SO$ | 6 | 21.2 ± 8.4 | 63 | 12 5 ± 4.2 | 50 | 9 4 ± 3 3 | 42 |
| $CaSO$ + $MgSO$ | 6 | 24 6 ± 9.2 | n.s. | 14 4 ± 6.0 | 58 | 10.5 ± 3.5 | 47 |
| $BaSO$ + $Na_2SO$ | 6 | 23 4 ± 26 7 | n.s. | 6.4 ± 2 7 | 25 | 4 9 ± 2.5 | 22 |
| $BaSO$ + $MgSO$ | 6 | 20.2 ± 12 2 | n.s. | 8.6 ± 1 6 | 34 | 5.4 ± 3.5 | 24 |
| Controls | 8 | 41 7 ± 12 3 | 100 | 17 7 ± 5.3 | 100 | 10.7 ± 3.9 | 100 |
| Sklabaryum + $Na_2SO$ | 8 | 39 4 ± 18.8 | n.s. | 10.2 ± 3.2 | 57 | 4 8 ± 1 0 | 44 |
| $BaSO$ + $N_2SO$ | 8 | 17 0 ± 6.5 | 41 | 5 5 ± 1 7 | 31 | 3 1 ± 0 8 | 29 |

Co tent of Sr in 1 femur times 20

Arithmetic mean ± standard error of the mean multiplied by t value for 95 confidence level

Difference is not statistically significant

statistically The decrease in the retention of ⁸⁵Sr was repeatedly significant only with sodium and barium sulphates. Calcium sulphate in one of the experiments was considerably more effective than magnesium and strontium sulphates

The differences in the average whole body retention of ⁸⁵Sr 48 hours after its administration were more marked and corresponded roughly with differences observed in the skeletal retention of ⁸⁵Sr There was no substantial difference between the effectiveness of the sulphates and Skiabaryum except in the case

sulphate. Exchange takes place in vitro between the ions of $Sr^{++}$ from the solution and ions of $Ca^{++}$ (or $Ba^{++}$) from calcium or barium sulphates. The ratio between the ions of $Sr^{++}$ in solution and on the surface of calcium sulphate (expressed in mole) is approximately 1 while a similar ratio in the case of barium sulphate is approximately 0.1 barium sulphate is therefore substantially more effective (LIESER & HILD 1959).

The present experimental results suggest, however that in vivo barium sulphate does not differ substantially from calcium sulphate or other sulphates, except strontium sulphate in which the lowest average effectiveness was observed. In this connection it is interesting that strontium was the least effective of the alkaline earth metals (except beryllium) in reducing the intestinal absorption of $^{85}$Sr when using in vivo perfusion techniques in rats (MRAZ 1962).

Skabaryum consists of talc, bentonite and sodium citrate, as well as of barium sulphate. Talc was without effect in the sorption of radiostrontium in decontamination experiments in vitro. The effect of bentonite decreased with increasing acidity (KNAJFL 1962); this also may be the reason why bentonite was without effect in vivo (COPP & GREENBERG 1944, MACDONALD et coll. 1952). Sodium citrate, which could be expected to stimulate intestinal strontium absorption, is present only in negligible quantities but according to WASSERMAN et coll. (1956) even 0.84 mM of sodium citrate per dose produced no increase in the intestinal absorption of $^{85}$Sr in rats.

A comparison of the effect of Skabaryum and barium sulphate alone in relation to $^{85}$Sr disclosed no marked difference. Skabaryum, combined with sodium sulphate, however was significantly less effective than a combination of barium and sodium sulphates. It may therefore be assumed that the presence of the other components in Skabaryum is not desirable for the purposes under consideration.

Sodium and magnesium sulphates are able to dilute the intestinal contents and stimulate their passage by inhibiting the reabsorption of water from the intestine. They form in the presence of stable strontium the less soluble strontium sulphate. It was therefore suggested by SCHUBERT (1955) that after accidental radiostrontium contamination, the treatment of choice would appear to be magnesium sulphate in combination with a laxative and possibly an antacid as well. However as indicated by WALSER et coll. (1961) unless carrier-strontium is given, the product of strontium and sulphate concentrations in plasma or urine cannot conceivably approach the solubility product of this salt. Hence the result observed in the case of carrier-free strontium may be due to an effect of absorbed sulphate, on urinary excretion of strontium, or due to impaired intestinal absorption of the strontium sulphate complex.

## Discussion

It is generally accepted that the appearance of ingested radiostrontium in bone is a reliable index of its absorption from the gut when animals are under similar physiologic conditions (WASSERMAN et coll 1956) The effect on the absorption of $^{85}$Sr of the sulphates tested was therefore estimated particularly according to the decrease in the skeletal retention of $^{85}$Sr when given orally Most of the experiments were based on a standard experimental design with equimolar amounts of sulphates administered to fasting rats in single doses, ten minutes after oral contamination with radiostrontium The sulphates used (0 8 mM per dose) would in man correspond to approximately 100 gram of substance and the volume of liquids to 0 7 l First-aid in practice could hardly be rendered earlier than 10 min after the accident

As a considerably lower retention of $^{85}$Sr was observed in the control animals given water immediately after radiostrontium (see Table 1) the possibility of a diminution of the $^{85}$Sr absorption by transfer of the strontium into distal parts of the intestine was considered A group of rats, given 2 ml drinking water immediately after oral contamination exhibited in another experiment significantly lower retention of Sr in comparison with another group in which an equal quantity of water was given ten minutes later The experiment was performed in spring and again several months later with as much as 8 ml water given immediately after radiostrontium without influencing its absorption (unpublished results) This may be explained by the observation of MICHON & QUILLOUX (1959) who in investigating the normal passage of radiostrontium through the alimentary tract of the rat noticed a remarkable retardation at the stomach level just in spring when the animals change fur a considerable amount of swallowed hair was present in the stomach of the rats dissected and absorption of ingested radiostrontium by the hair was presumed An accelerated passage of radiostrontium through the intestine after the administration of several millilitres of water was also noted

The decontamination efficacy of the various sulphates tested did not differ substantially although their mechanism of action was not identical.

Whole body counting at 24 hours after the administration of radiostrontium indicated no definite effect probably because faeces containing the unabsorbed $^{85}$Sr were not yet excreted The retention of $^{85}$Sr 48 hours after the administration of sulphates decreased by 30 to 70 % in comparison with the controls

Barium sulphate mainly owing to its sorptive properties, minimizes the absorption of radiostrontium Regarding effectiveness in vivo it is significant that the solubility of sulphates decreases in the order calcium sulphate > strontium sulphate > barium sulphate Barium and strontium sulphate are isomorphous whereas calcium sulphate is not neither with barium nor strontium

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## Discussion

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& USHAKOVA (1937) administered magnesium sulphate (15 mg per dose) to rats repeatedly for twelve days without any noticeable effect. TAYLOR et coll. (1962) reported that the percentage absorption of $^{85}$Sr in rats given orally 300 µg of $SO_4$ ions did not differ significantly in comparison with the controls. STANKOV (1953) stated that the skeletal retention of $^{89}$Sr in rats previously fed with barium sulphate, was 1.6 to 1.7 times lower than in the control animals. The administration of the barium sulphate first after the radiostrontium was without substantial effect.

The results of various authors are clearly at variance. This may be explained by the effect of sulphates in relation to their dose (cf part III to be published later in this journal).

It was assumed in administering a combination of sulphates that the effectiveness of a low-soluble sulphate could be increased by the addition of excess sulphate ions in the form of sodium or magnesium sulphates. It is known that after the addition of a soluble sulphate to barium sulphate in vitro there is a decrease in the concentration of free $Ba^{++}$ ions, which compete with the adsorption of $Sr^{++}$ ions. In this way the total capacity of barium sulphate for the binding of radiostrontium is markedly increased while the rate of adsorption remains unchanged. On the other hand after the addition of sodium sulphate in a millimolar concentration to a relatively more soluble calcium sulphate, the solubility of the latter remains practically unchanged (BEZÁK 1963) and therefore an increase of its effect could hardly be expected.

The results of the experiments carried out in rats are in accordance with this presumption. There was no significant increase in the effectiveness of calcium sulphate after the addition of an equimolar amount of sodium or magnesium sulphates. However the average effectiveness of barium sulphate was significantly improved by this addition and the variance of the average values of $^{85}$Sr retention was also reduced. This means higher effectiveness and reliability in treatment.

## Appendix (BY Z. ROTH)

### Comparison of the average $^{85}$Sr retention in several groups of animals

When comparing the average values of whole-body and the skeletal $^{85}$Sr retention among various groups of animals, the analysis of variance could not always be used owing to statistically significant differences regarding the variance in different groups in some of the experiments. This was tested by the Bartlett test according to the formula

$$\chi^2 = 2.303 \left( f \log s^2 - \sum_{i=1}^{k} f_i \log s_i^2 \right)$$

A synergic stimulating action of the absorbed sulphate ions could thus be presumed with both the sulphates, with magnesium sulphate, also from the influence of *magnesium* ions. CATSCH & MELCHINGER (1959) described a decrease in the skeletal retention of intraperitoneally injected radiostrontium in rats (by 30 to 40 %) if various compounds containing magnesium were administered simultaneously. NELSON et coll. (1963) observed in their experiments with mice that the effect of magnesium sulphate injected intraperitoneally on the retention of radiostrontium was of the same order of magnitude as that of strontium chloride. When CLARK & SMITH (1962) injected magnesium sulphate the elimination of $^{85}$Sr increased in rats that had been given the isotope either one or thirty days before treatment. Oral administration of magnesium chloride increased the urinary excretion of $^{85}$Sr although the faecal $^{85}$Sr decreased. CLARK & SMITH followed only the elimination of radiostrontium. KROLL (1960) observed an increase in urinary $^{85}$Sr after the intraperitoneal injection of sodium and ammonium sulphates and magnesium chloride by about 15 % and with magnesium sulphate by 49 %. When sodium sulphate was administered orally but simultaneously with $^{85}$Sr a decrease in the skeletal retention of radiostrontium by 60 % and a fourfold increase in urinary excretion was described by the same author. He therefore assumed that the intestinal resorption of radiostrontium increased as well and that this might have been the effect of absorbed sulphate ions. In dogs the rate of urinary radiostrontium excretion during the infusion of sodium sulphate increased several times (WALSER et coll. 1961).

When administering sodium and magnesium sulphates we were unable to differentiate between the results achieved with these and the average effect of other sulphates investigated. Although magnesium sulphate caused diarrhoea in two groups of rats, it was ineffective in one of the experiments. The retention of $^{85}$Sr after the administration of sodium sulphate decreased by 37 to 52 % and after magnesium sulphate by 43 to 59 %. This is in agreement with the results of KROLL, and with the observation of MACDONALD et coll. (1952) that the ingestion of magnesium sulphate by rats, immediately following the administration of strontium by stomach tube, decreased its skeletal accumulation from 16 % to 5 %; the effect of sodium sulphate was only slightly lower.

The present results were obtained in rats after administering 0.8 mM per dose of sulphates. MACDONALD et coll. (1955) administered sodium sulphate in a dose four times higher after oral contamination with $^{90}$Sr—$^{90}$Y but the resulting decrease in radiostrontium retention was only 34 % in comparison with the controls. JONES (1955), who similarly investigated sodium and calcium sulphates in doses that have not been indicated in detail, doubted whether the decrease achieved in radiostrontium resorption was significant. RUBANOVSKAIA

## SUMMARY

The average retention of [illegible]Sr given orally decreased when various sulphates were administered immediately or ten minutes later. Excepting strontium sulphate which proved least effective there was no substantial difference in their effectiveness. When combination of barium sulphate with sodium or magnesium sulphates was used the results were significantly better than with each sulphate alone.

## ZUSAMMENFASSUNG

Die durchschnittliche Aufspeicherung von Radiostrontium wurde ermindert wenn verschiedene Sulfaten sofort oder 10 Minuten nach der mundlichen Verabreichung von [illegible]Sr gegeben wurden. Ausser Strontiumsulfat, das sich am wenigsten wirksam erwies, war kein grosser Unterschied merkbar. Wenn man Bariumsulfat zusammen mit Natrium- oder Magnesiumsulfat gab, wurden die Resultate aber beachtlich besser als wenn man nur ein Sulfat benutzte.

## RÉSUMÉ

La fixation moyenne de [illegible]Sr administré par la bouche diminue quand on administre divers sulfates immédiatement ou dix minutes plus tard. Il n'y a pas de différence dans leur efficacité, excepté le sulfate de strontium qui s'est montré le moins efficace. On obtient des résultats notablement meilleurs quand on emploie une association de sulfate de baryum et de sulfate de sodium ou de magnésium qu'avec chacun de ces sulfates isolément.


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where $k$ is the number of variances compared, $s_i^2$ the variance in the i-th groups, $f_i$ the degrees of freedom of the variance $s_i^2$, $f = \sum_{i=1}^{k} f_i$, $s^2 = \left(\sum_{i=1}^{k} f_i s_i^2\right)/f$ and $c = 1 + \left[\sum_{i=1}^{k} (1/f_i - 1/f)\right]/3(k-1)$. This criterion has $k-1$ degrees of freedom.

The comparison of average values in the various groups was made by Duncan's multiple range test for heteroscedastic groups of data (DUNCAN 1957). Differences between the two means compared were adjusted by a factor $k_{ij}$, where $k_{ij} = \sqrt{\frac{2}{s^2_{\bar{x}_i} + s^2_{\bar{x}_j}}}$ for i-th and j-th group compared.

When testing differences between the compared means, the Duncan's method had to be modified: the use of the common residual variance as described by DUNCAN was not possible owing to the heteroscedasticity of the results. In order to assess the sufficiently correct critical value of Duncan's $r_p$, a method was used analogic to the procedure of WELCH (1949) for the t-test for two groups of differences of variances. For each pair of means we determined the given $p$ (i. e. the difference in ranks of values compared according to their sizes) and a respective value $r_p$ for the number of degrees estimated according to the formula

$$f' = \frac{(s^2_{\bar{x}_i} + s^2_{\bar{x}_j})^2}{\frac{s^4_{\bar{x}_i}}{f_i} + \frac{s^4_{\bar{x}_j}}{f_j}}$$

where $f_i$ and $f_j$ are degrees of freedom of the variance. The test procedure was as follows: when the absolute value of the adjusted difference of both marginal values was lower than the critical value $r_p$, we determined whether another adjusted difference of two means lying between both marginal values was higher than $r_p$. The critical value was then taken for the same $p$ but in general not for the same $f'$.

This procedure is not entirely correct but approximately equals the Welch procedure for the t-test. It may be concluded therefore that in cases where a significant difference was found between some pair of means the true significance level does not differ too much from the given test value.

The computed average values were completed by calculation of their 95% confidence intervals, according to the formula

$$x_{1,2} = \bar{x} \pm t_{0.05}\, s_{\bar{x}}$$

where $x_1$ and $x_2$ are limits of the confidence interval for the 95% confidence level and $t_{0.05}$ the critical value of the Student's $t$.

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# RADIOISOTOPE SCANNING OF THE MEDIASTINAL LYMPHATICS IN ANIMALS

by

S HO CHOI, W GORDON F R SHEEHAN and M A BENDER

The delineation of the lymphatic drainage of the lung should be of value in the diagnosis and treatment of pulmonary lesions. An attempt was therefore made to develop a system for defining lymphatic drainage of the lung parenchyma in animals, which might be applicable to human subjects. The literature revealed that HAHN (1953 1956) introduced $^{198}$Au into the tracheobronchial tree for the treatment of bronchogenic carcinoma with no systemic ill effects. SAGE & GOZUN (1958) used $^{198}$Au injected into the subcutaneous tissues to delineate regional lymph nodes. Similar work was done by other authors (HULTBORN et coll. 1955 LEBORGNE et coll. 1955) The present authors decided to inject $^{198}$Au into the lung parenchyma of animals and to study its spread through the mediastinum.

*Material and Method* In initial experiments, 10 $\mu$C $^{198}$Au of average particle size 0 003 $\mu$ were injected directly into the lungs of rabbits at thoracotomy and the animals were sacrificed 2 hours later Tissue samples, each of 1 g were taken from (1) the injection site (2) the corresponding site in the opposite

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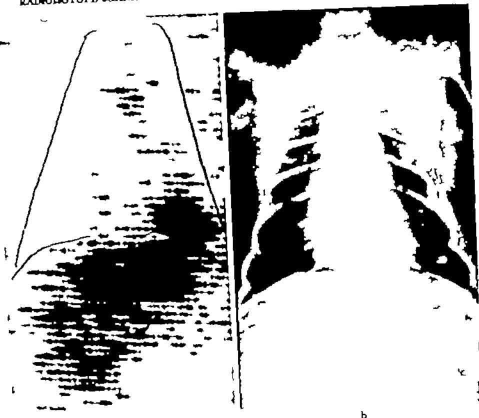


Fig. 3. ) Scintigram, six day after injection of 25 μC Au into lef lower lung b) Chest roentgenogram.

lung (3) the region of the carina, (4) the right superior mediastinum, (5) the left superior mediastinum and (6) the liver and were stored in test tubes for later assay in a well scintillation counter. These experiments revealed a pickup of ¹⁹⁸Au by the lymph nodes in the mediastinum but were terminated at this point because the small anatomy presented technical problems in scanning.

Further experiments were carried out in dogs weighing between 9 to 13 kg. Each animal was anesthetized with intravenous phenobarbital. A 27 gauge needle attached to a nylon tube was passed through the wall of a peripheral bronchus via a bronchoscope and 25 μC of ¹⁹⁸Au in 8 ml water were injected into the lung. Sufficient time must be allowed for the radioactive material to enter the lymphatics; it will not however be demonstrated by scanning beyond certain degree of decay and it is necessary to scan not later than 2 to 3 half lives from the time of injection. Scintigrams were obtained of the dog's thorax t intervals over a 3 to 10 day period. A previously described instrument was

a b

Fig 1 a) Scintigram, seven day after jection of 25 μC MA int left l wer lung b) Chest roent genogram

b

Fig a) Scintigram, eight day fter jection of 25 μC MA t left lower lung b) Chest roent genogram

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used and the average scanning took 30 to 45 minutes The animal was sacrificed after a period of 8 to 21 days and tissue samples similar to those in the rabbit were taken for later assay in a well scintillation counter and for histologic examination

## Results

Satisfactory scintigrams of the pickup of radioactive gold $^{198}$Au by the mediastinal lymphatics and lymph nodes were obtained 6 to 8 days after injection. *Figs 1 and 3 show scintigrams and roentgenograms of the chests of dogs.* Activity was found at the site of injection in the mediastinum and in the liver The differentiation of the radioactivity of the right half of the mediastinum from the left half is unsatisfactory in the dog because of the small size of the animal and the limited resolution of the scanner *Counts from the specimens* removed disclosed 12 % of total activity at the time of count at the site of injection which was the left lower lobe none in the contra lateral lung 1 6 % at the carina 2 5 % in the right superior mediastinum 0 3 % in the left superior mediastinum and 0 27 % in the liver It should be pointed out that 80 % of the total activity was present in the whole liver There was no clinical or histologic *evidence of damage of tissue at the site of injection or in the mediastinum* from $^{198}$Au

## Acknowledgement

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## SUMMARY

A method of studying the lymphatic drainage of the lung of the dog by radioisotopic scanning is described The procedure may be applicable in human subjects.

## ZUSAMMENFASSUNG

Eine Methode zum Studium der Lymphwege der Lunge des Hundes mit Hilfe von radioaktiven Isotopen wird beschrieben Ein ähnliches Vorgehen könnte am Menschen benutzt werden

## RÉSUMÉ

L auteur décrit une méthode d étude du drainage lymphatique du poumon du chien par scanning radio-isotopique Cette technique pourrait être appliquée à des sujets humains.

Other cases of cancer of the oesophagus examined during this period were not included in the present investigation either because the roentgenograms were unsatisfactory in quality or because the biopsy specimens had not been large enough to permit histologic grading of the tumour or because the biopsy specimens had not been secured until after radiotherapy had been started.

All the patients received radiotherapy no cases of cancer of the hypopharynx were included The slides and roentgenograms were routine preparations the biopsy specimens were embedded in paraffin sectioned (4 μ) and stained with haematoxylin-eosin and van Gieson s stain.

The tumours were graded histologically according to BRODERS (1920 1922, 1926 1928) and interpreted roentgenologically according to length of tumour degree of stricture of oesophagus, diffuseness or sharpness in outline of the upper part of the tumour and according to the presence or absence of ulceration and polypoid changes in the area of the tumour as seen in films obtained from different angles. In addition notes were made of the presence of any inflammation in the biopsy specimens, and the duration of the symptoms before the establishment of the diagnosis was correlated with the degree of differentiation of the tumour and the roentgen findings. The material was first examined separately by the radiologists and the pathologist and afterwards jointly by all three.

## Results

The cases are classified according to histologic grade in Table 1 Males were more common in groups II III and IV as well as in the entire material, while the age distribution in the respective groups in the main was uniform. The duration of the lesions, as reckoned from the onset of initial symptoms did not vary appreciably from one histologic group to another or with the roentgen findings.

The only correlation found between the histologic grade and the roentgen appearance of the tumours was that the roentgenologic outline of the upper part of the highly differentiated tumours (grade I) tended to be more clearly defined than in the undifferentiated (grade IV) (Figs 1 and 2) It should, however be observed that the range of variations was fairly wide in all the groups, especially in groups II and III (Table 2) In only one of the cases of grade IV however was the upper part of the tumour clearly (+ + +) defined in the roentgenogram and the histologic examination revealed marked inflammatory changes in the area affected by the tumour and varicose veins in the submucosal layer

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# SQUAMOUS EPITHELIAL CARCINOMA OF THE OESOPHAGUS

## Roentgenologic and histologic investigations

by

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The treatment of squamous epithelial carcinoma of the oesophagus presents many problems and the percentage of cures achieved by surgery or radiotherapy is low. Roentgenologic demonstration of the tumour generally offers no difficulties when symptoms exist. In view of the wide variety of the roentgen appearances in cancer, it was considered of interest to investigate whether the characteristics of the roentgenogram vary with the degree of differentiation of the tumour, in analogy with what NORMAN (1950) found in cases of adenocarcinoma of the body of the uterus. The primary roentgen findings in cases of squamous epithelial carcinoma of the oesophagus, and the histologic features of biopsy specimens excised before treatment, were studied for any inter-relationship.

*Materials and Methods.* The material is represented by 100 cases of squamous epithelial carcinoma of the oesophagus seen during the years 1944—1958

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Table 1 *(cont.)*

*cases) according to the histologic grades*

| Length of tumour (cm) | Stricture (— → +++) | Ulceration (— → +++) | Polypoid changes (— → +++) | Upper outline (— → +++) |
|---|---|---|---|---|
| 6.8 (2.5—9.5) | ++(+) | + | + | ++(+) |
| 7.5 (3.5—12) | ++ | + | + | ++ |
| 7.1 (4—12) | ++ | + | +(+) | +(+) |
| 7.2 (5—10.5) | ++ | + | + | (+) |

## Discussion

The size of the dose in radiotherapy of squamous epithelial carcinoma of the oesophagus is dictated in part by the degree of histologic differentiation of the tumour. The possibility of local healing is said to be greater in anaplastic cancer treated with radiation than in cases of more differentiated tumours. It is, however, often difficult for the pathologist to grade the tumour from the diagnostic biopsy specimen, and these specimens moreover do not always provide representative tumour appearances (MARTZLOFF 1927). Such biopsy specimens represent, however, the only material available for histologic grading before radiotherapy has been started.

It was consequently considered worthwhile to make a study of a large series, by uniform methods, for any correlation obtainable between the degree of histologic differentiation of the tumours and their roentgenographic features.

It was hoped that by the combined use of these two methods it might be possible to obtain a satisfactory estimate of the degree of maturation in given cancer cases.

Roentgenologically, the histologic groups of the tumours differed but slightly from one another in length, degree of stricture of the oesophagus and occurrence of ulceration and polypoid changes. The upper part of the highly differentiated tumours (grade I) tended, however, to be much more sharply outlined than the undifferentiated ones (grade IV), probably because of the gross fungating form that is often assumed by the highly differentiated squamous epithelial tumours. WU YING-KAI et coll. (1958) compared the gross appearances of squamous epithelial carcinomas of the oesophagus with

Table 1

*Classification of the material (100*

| Histologic grades | Number of cases | Males/ Females | Age in years | Length of history (months) |
|---|---|---|---|---|
| I | 14 | 5/9 | 69 4 (46—84) | 3.3 (1/2—6) |
| II | 28 | 16/12 | 68.2 (47—86) | 3 3 (1—12) |
| III | 42 | 31/11 | 67.5 (39 81) | 3.9 (1—9) |
| IV | 16 | 13/3 | 71 1 (43—88) | 4.2 (1/2—12) |

Table 2

*Distribution of the case material according to histologic grading as compared with the roentgenographic definition of the upper part of the tumours*

| Histologic grades | Upper outline of tumour (— + ++ +++) | Number of cases |
|---|---|---|
| I | +++ | 8 |
| | ++ | 5 |
| | + | 0 |
| | — | 1 |
| | Total | 14 |
| II | +++ | 7 |
| | ++ | 12 |
| | + | 6 |
| | | 3 |
| | Total | 28 |
| III | +++ | 10 |
| | ++ | 10 |
| | + | 18 |
| | | 4 |
| | Total | 42 |
| IV | +++ | 1 |
| | ++ | 1 |
| | + | 6 |
| | — | 8 |
| | Total | 16 |

Table 1 *(cont.)*

*cases) according to the histologic grades*

| Length of tumour (cm) | Structure (— → +++) | Ulceration (— → +++) | Polypoid changes (— → +++) | Upper outline (— → +++) |
|---|---|---|---|---|
| 6.8 (2.5—9.5) | ++(+) | + | + | ++(+) |
| 7.5 (3.5—12) | ++ | + | + | ++ |
| 7.1 (4—12) | ++ | + | +(+) | +(+) |
| 7.2 (3—10.5) | ++ | + | + | (+) |

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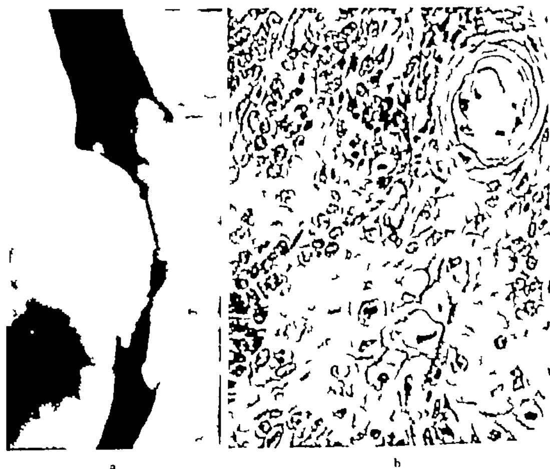


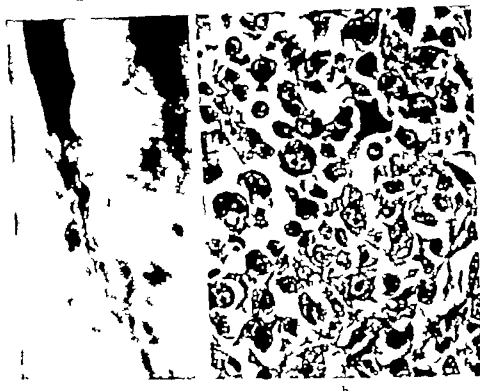
Fig. 1. a) Long, markedly stenosing oesophageal carcinoma, well defined both orally and aborally. b) Squamous cell carcinoma, grade I. Distinct characteristics of squamous cell carcinoma and cornification. Htx-eosin × 400.

the histologic grade of the tumours (according to BRODERS) and found that all tumours of the fungating type belonged to grades I–III.

It thus appears that the histologic grade of a squamous epithelial carcinoma of the oesophagus cannot be correlated with its roentgen appearances, with the exception that if the upper part of the tumour is well defined in the roentgenogram the tumour is often highly differentiated and if diffuse it is undifferentiated.

## SUMMARY

Squamous epithelial carcinoma of the oesophagus was graded histologically from acceptable diagnostic tissue specimens, excised before radiation treatment, in a material of 100 cases. The upper part of the highly differentiated tumour tended to be well outlined in the roentgenograms. This was the only correlation evident between the histologic grade and the roentgen appearance of the tumour.



b

Fig. 2. ) Moderately narrowing oesophageal carcinoma with diffuse oral outline. b) Squamous cell carcinoma, grade IV. Undifferentiated cells with mitoses; several multi-nucleated cells. Hem-eosin. 500.

## ZUSAMMENFASSUNG

In hundert Fällen von Plattenepithelcancer im Oesophagus, histologisch eingeteilt an Biopsiematerial bevor radiologische Behandlung angewandt wurde, zeigten die hoch differenzierten Tumore im Gegensatz zu den undifferenzierten eine Neigung zu distinkter proximaler Begrenzung auf dem Röntgenfilm. Diese war die einzige Korrelation zwischen histologischer Struktur und Röntgenbefund.

## RÉSUMÉ

Les auteurs ont établi le classement histologique de 100 cas d'épithélioma spino-cellulaire de l'oesophage en se basant sur des pièces biopsiques acceptables prélevées avant le début de la radiothérapie. Sur les radiographies, la partie supérieure des tumeurs hautement différenciées est en général bien délimitée. C'est la seule corrélation qui pu être mise en évidence entre le degré de différenciation histologique et l'aspect radiologique de la tumeur.

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# SENSITIZATION AND RADIATION RESPONSE IN CASES WITH CARCINOMA OF THE UTERINE CERVIX

## Investigations in 720 cases treated at Radiumhemmet 1954—1961

by

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Much discussion has centred around the question of whether or not curability in successfully irradiated carcinoma of the uterine cervix is associated with some specific sensitivity of the tumour or the normal cell populations to ionizing radiation. Many attempts have been made to evolve methods by which the radiosensitivity of tumours might be recognized before or during radiotherapy (For reviews of the literature cf. Merrill 1958, Davis 1960, Darcis 1962.) Some writers have suggested that radiosensitivity may be predicted by studying the maturation stage of tumours in pretreatment surgical biopsy specimens (Martzloff 1923, Novak 1954) or by determining the DNA content of malignant cell nuclei (Richards & Atkin 1959).

Glucksmann et coll. (Glucksmann & Spear 1945, Glucksmann 1946, 1949, 1958) reported investigations of serial biopsies of the tumour area during radiotherapy. Good radiation response, as determined on the seventh day

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after the initial insertion of radium was characterized by the absence of normal mitosis in tissue sections, reduction of resting cells below 30 % and increased differentiation and degeneration.

GRAHAM (1947) presented data suggesting that cytologic findings in vaginal smears taken during radiotherapy could be correlated with clinical outcome in individual cases. Morphologic changes in non malignant squamous epithelial cells, such as vacuolisation of the cytoplasm nuclear changes, increase in cell size and multinucleation were used as indicators of the host's response to irradiation In a later paper (GRAHAM & GRAHAM 1955) it was reported that among patients whose tumours showed good response, by which was meant that 75 % or more of the benign epithelial cells displayed radiation changes, 65 % survived 5 years without evidence of disease. Poor response — less than 60 % of cells with radiation changes — was associated with low radiocurability and only 8 % of these patients were well after 5 years. In other reports the limits of response (percentages of non malignant epithelial cells with radiation changes) were expressed as 70 or more for good response and 69 or less for poor response (cf GRAHAM & GRAHAM 1957)

Radiation response (RR) could be determined before the completion of treatment viz after 1 000 or 2 000 R of external radiation or after a single radium application (GRAHAM 1958)

GRAHAM & GRAHAM (1953) further claimed that the host's radiosensitivity could be predicted by morphologic studies of non malignant cells in vaginal smears prior to radiotherapy In differential counts of at least 100 normal epithelial cells the presence of 10 % or more basal cells with dense finely vacuolated cytoplasm was considered to correlate well with a 5-year cure. This test which was called the sensitization response (SR) was thought possibly to be related to an immunologic mechanism and heightened sensitivity to ionizing radiation (GRAHAM and GRAHAM et coll 1953 1954 1960, 1963)

Because of its potential value in the clinical management of carcinoma of the cervix, the Grahams work stimulated intensive research in many centres. Some workers confirmed their observations on RR and SR (ROTH 1951 NIELSEN 1952 MEILING 1953 KOHN 1954 von HAAM 1954 ÖSTBERG & DARCH 1956 GOMPEL 1958 KJELLGREN 1958 MESELT 1958 MONTALVO RUIZ & JIMENEZ TEBAR 1959 RAKOFF 1959 AGNEW et coll 1960 ARRIGHI 1960 SHIER 1961 GRATTAROLA & LUCIANI 1962 MERRILL 1962, MOORE et coll. 1963 SIRACKI et coll. 1963) Others failed however to obtain equally good results (BESSERER & SMOLKA 1952 LIMBURG et coll. 1952 RUMMEL 1953 MOHR 1954 SHIER 1954 WAHI & GUPTA 1955 SMOLKA & SOOST 1956 HERMAN et coll 1959 JONES et coll 1959 LANIER & WIKLE 1959 MENGERT

1959 CARTER 1960, DONLAN & PLATT 1960 JORDAN 1960 KAUFMANN & KAHN 1960 SILVERMAN et coll. 1961 KANGAS 1962, PAULLADA et coll. 1962, ZERNE & MORRIS 1962 FEINER & GARIN 1963 RAURAMO & KANGAS 1964)

The radiation response has been studied in 720 cases and the sensitization response in 681 cases at Radiumhemmet. The investigation began in 1954 and the results have recently been evaluated.

## Material and Methods

The members of the staff who were to be responsible for preparing smears and reading the RR and SR were sent to the Grahams laboratory for six months' training before the investigation was begun. This was done in order to make them fully familiar with the interpretation of the cytologic changes (vacuolization of cytoplasm, nuclear changes, increase in cell and nuclear size, multinucleation) and thus enable them to reproduce in detail the Graham methods of evaluating RR and SR (GRAHAM 1947 GRAHAM & GRAHAM 1953)

The patients were treated from 1954 through 1961 As smears for evaluation of RR had to be taken at frequent intervals, the series was confined to patients living in or near Stockholm. Follow-up was made to the end of 1962 in every instance.

The histologic type of malignancy was obtained in every case. In 686 cases the diagnosis was squamous cell carcinoma, of which 282 were poorly differentiated, 327 moderately and 34 highly differentiated 25 showed areas of minimal invasion 2 were classified as carcinoma in situ and 16 of a mucoepidermoid type In the remaining 34 cases the diagnosis was adenocarcinoma.

Clinical classification of the tumours was as follows 2 stage 0 (carcinoma in situ) 203 stage I 225 stage II A, 175 stage II B 86 stage III and 24 stage IV The initial diagnosis of carcinoma of the cervix was altered to carcinoma of the uterine body and cervix in four of the remaining 5 cases and to carcinoma of the vagina in the fifth case.

Four hundred and twelve patients were premenopausal and 286 were postmenopausal surgical castration had been carried out some years previously in 17 and the carcinoma was associated with pregnancy in 5 patients.

The number of patients who were alive at the end of 1962 or in those from 1958, at the end of 1963 are recorded in Table 1 Thus, of the 720 patients in whom RR was investigated, 487 were followed up for 5 years or more

It is the custom at Radiumhemmet when reporting results of treatment in malignant neoplasms to attribute all deaths during the observation period to the disease Survival percentages are based in this report on the total number of cases observed during the period in question.

Table 1

*Treated cases (720) of carcinoma of the cervix investigated for radiation response*

| Year of treatment | No of cases | Deaths | Numbers of survivals | Percentage |
|---|---|---|---|---|
| 1954 | 120 | 54 | 66 | 55 0 |
| 1955 | 75 | 29 | 46 | 61.3 |
| 1956 | 78 | 22 | 56 | 71.8 |
| 1957 | 106 | 43 | 63 | 59 4 |
| 1958 | 108 | 43 | 65 | 60.2 |
| 1959 | 81 | 32 | 49 | 60.5 |
| 1960 | 69 | 15 | 54 | 78.3 |
| 1961 | 83 | 10 | 73 | 88.0 |
| Total of cases | 720 | 248 | 472 | 65 6 |

Alive t the end of 1962 except fo cases from 1958 in which survival was calculated up to the end of 1963

The records of treatment were available for analysis in 719 of the 720 cases and in the remaining case the treatment chart had been lost. Of these 719 cases 575 received the standard Stockholm treatment (Ra I and 3 weeks later Ra II followed by roentgen irradiation) Roentgen therapy was begun prior to Ra I in 132 cases in 31 of which it was interrupted before and in 101 after the initial application of radium The complementary roentgen dose was given after Ra II in all 132 cases. Twelve cases received no roentgen therapy in association with radium.

## Sensitization response

The sensitization response (SR) was determined in 658 of the 720 cases in which radiation response (RR) subsequently was analyzed in 39 of the remaining 62 cases pretreatment smears were not available and in 23 cases the smears were unsatisfactory Significant or good SR was defined according to GRAHAM & GRAHAM (1953) as presence of SR in 10 % or more of the non malignant epithelial cells Poor SR thus implied 9 % or less incidence of SR At least 100 non malignant cells were counted for each test.

SR was good in 137 (20 8 %) of the 658 cases and was poor in 521 cases. The survival rates in the 449 cases in which the observation period was 5 years or more are given in Table 2 Of the 95 cases with good SR 54 cases, (56 8 %) were alive after 5 years Among the 354 cases with poor SR 224 (63 3 %) were alive after 5 years These figures suggest that the SR was not a reliable prognostic index in radiologically treated carcinoma of the cervix.

Table 2

*Sensitization response correlated to > 5-year-follow-up and tumour stage*

| Clinical stage of carcinoma | Good SR | | | Poor SR | | | All cases |
|---|---|---|---|---|---|---|---|
| | Total | Alive | Dead | Total | Alive | Dead | |
| I | 10 | 7 | 3 | 114 | 97 | 17 | 124 |
| II A | 35 | 24 | 11 | 113 | 75 | 38 | 148 |
| II B | 29 | 13 | 16 | 76 | 39 | 37 | 105 |
| III | 17 | 8 | 9 | 40 | 11 | 29 | 57 |
| IV | 3 | 2 | 1 | 10 | 1 | 9 | 13 |
| Cancer of uterine body and cervix | 1 | | 1 | 1 | 1 | | 2 |
| Total | 95 | 54 | 41 | 354 | 224 | 130 | 449 |

## Maximum radiation response

### *A Radiation response (RR) and survival*

The general opinion being held that maximum RR occurs 12 to 14 days after the initial application of radium (GRAHAM 1958, DAVIS et coll. 1960) the response on these days was first compared with survival.

*RR at 12 to 14 days after Ra I in cases with standard treatment and 5 year follow-up*
Of the 368 patients who were observed for at least 5 years after treatment by the standard Stockholm technique, 73 failed to attend for examination on the 12th to 14th days, and the smears taken during these critical days were in 35 cases unsatisfactory for cytologic examination. RR in the remaining 260 patients is correlated with the results of the 5-year follow-up in Table 3. It is seen that in 235 of the 260 patients the RR at 12 to 14 days was less than

Table 3

*Radiation response 12 to 14 days after radium I treatment correlated to 5 to 8-year follow-up*

| Radiation response | At follow-up | | |
|---|---|---|---|
| | Alive | Dead | Total |
| 70—100 | 15 | 10 | 25 |
| 0— 69 % | 162 | 73 | 235 |
| Total | 177 | 83 | 260 |

Table 1

*Treated cases (720) of carcinoma of the cervix investigated for radiation response*

| Year of treatment | No of cases | Deaths | Numbers of survivals | Percentage |
|---|---|---|---|---|
| 1954 | 120 | 54 | 66 | 55 0 |
| 1955 | 75 | 29 | 46 | 61.3 |
| 1956 | 78 | 22 | 56 | 71.8 |
| 1957 | 106 | 43 | 63 | 59.4 |
| 1958 | 108 | 43 | 65 | 60.2 |
| 1959 | 81 | 32 | 49 | 60.5 |
| 1960 | 69 | 15 | 54 | 78.3 |
| 1961 | 83 | 10 | 73 | 88.0 |
| Total of cases | 720 | 248 | 472 | 65 6 |

Alive at the end of 1962 except for cases from 1958 in which survival was calculated up to the end of 1963

The records of treatment were available for analysis in 719 of the 720 cases and in the remaining case the treatment chart had been lost. Of these 719 cases 575 received the standard Stockholm treatment (Ra I and 3 weeks later Ra II followed by roentgen irradiation) Roentgen therapy was begun prior to Ra I in 132 cases in 31 of which it was interrupted before and in 101 after the initial application of radium The complementary roentgen dose was given after Ra II in all 132 cases. Twelve cases received no roentgen therapy in association with radium.

## Sensitization response

The sensitization response (SR) was determined in 658 of the 720 cases in which radiation response (RR) subsequently was analyzed in 39 of the remaining 62 cases pretreatment smears were not available and in 23 cases the smears were unsatisfactory Significant or good SR was defined according to GRAHAM & GRAHAM (1953) as presence of SR in 10 % or more of the non malignant epithelial cells Poor SR thus implied 9 % or less incidence of SR At least 100 non malignant cells were counted for each test

SR was good in 137 (20 8 %) of the 658 cases and was poor in 521 cases. The survival rates in the 449 cases in which the observation period was 5 years or more are given in Table 2 Of the 95 cases with good SR 54 cases, (56 8 %) were alive after 5 years. Among the 354 cases with poor SR 224 (63 3 %) were alive after 5 years These figures suggest that the SR was not a reliable prognostic index in radiologically treated carcinoma of the cervix.

Table 2

*Sensitization response correlated to > 5-year-follow-up and tumour stage*

| Clinical stage of tumours | Good SR Total | Alive | Dead | Poor SR Total | Alive | Dead | All cases |
|---|---|---|---|---|---|---|---|
| I | 10 | 7 | 3 | 114 | 97 | 17 | 124 |
| II-A | 35 | 24 | 11 | 113 | 75 | 38 | 148 |
| II-B | 29 | 13 | 16 | 76 | 39 | 37 | 105 |
| III | 17 | 8 | 9 | 40 | 11 | 29 | 57 |
| IV | 3 | 2 | 1 | 10 | 1 | 9 | 13 |
| Cancer of uterine body and cervix | 1 | | 1 | 1 | 1 | | 2 |
| Total | 95 | 54 | 41 | 354 | 224 | 130 | 449 |

## Maximum radiation response

### *A Radiation response (RR) and survival*

The general opinion being held that maximum RR occurs 12 to 14 days after the initial application of radium (GRAHAM 1958 DAVIS et coll. 1960) the response on these days was first compared with survival.

*RR at 12 to 14 days after Ra I in cases with standard treatment and 5 year follow-up* Of the 368 patients who were observed for at least 5 years after treatment by the standard Stockholm technique, 73 failed to attend for examination on the 12th to 14th days, and the smears taken during these critical days were in 35 cases unsatisfactory for cytologic examination. RR in the remaining 260 patients is correlated with the results of the 5-year follow-up in Table 3 It is seen that in 235 of the 260 patients the RR at 12 to 14 days was less than

T ble 3

*Radiation response 12 to 14 days after radium I treatment correlated to 5 to 8-year follow-up*

| Radiation response | At follow-up Alive | Dead | Total |
|---|---|---|---|
| 70—100 % | 15 | 10 | 25 |
| 0— 69 % | 162 | 73 | 235 |
| Total | 177 | 83 | 260 |

Table 1

*Treated cases (720) of carcinoma of the cervix investigated for radiation response*

| Year of treatment | No of cases | Deaths | Numbers of survivals | Percentage |
|---|---|---|---|---|
| 1954 | 120 | 54 | 66 | 55.0 |
| 1955 | 75 | 29 | 46 | 61.3 |
| 1956 | 78 | 22 | 56 | 71.8 |
| 1957 | 106 | 43 | 63 | 59 4 |
| 1958 | 108 | 43 | 65 | 60.2 |
| 1959 | 81 | 32 | 49 | 60.5 |
| 1960 | 69 | 15 | 54 | 78.3 |
| 1961 | 83 | 10 | 73 | 88.0 |
| Total of cases | 720 | 248 | 472 | 65.6 |

Alive at the end of 1962 except for cases from 1958, i which survival was calculated up to the end of 1963

The records of treatment were available for analysis in 719 of the 720 cases and in the remaining case the treatment chart had been lost Of these 719 cases 575 received the standard Stockholm treatment (Ra I and 3 weeks later Ra II followed by roentgen irradiation) Roentgen therapy was begun prior to Ra I in 132 cases in 31 of which it was interrupted before and in 101 after the initial application of radium. The complementary roentgen dose was given after Ra II in all 132 cases Twelve cases received no roentgen therapy in association with radium.

## Sensitization response

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SR was good in 137 (20 8 %) of the 658 cases and was poor in 521 cases. The survival rates in the 449 cases in which the observation period was 5 years or more are given in Table 2 Of the 95 cases with good SR 54 cases, (56 8 %) were alive after 5 years. Among the 354 cases with poor SR 224 (63 3 %) were alive after 5 years. These figures suggest that the SR was not a reliable prognostic index in radiologically treated carcinoma of the cervix

Table 5

*Radiation response maximum during the whole treatment period and survival*

| Radiation response (%) | Number of patients alive at follow-up (years) > 5 | > 1 | Percentages of patients alive at follow-up (years) > 5 | > 1 | Number of deaths at follow-up (years) > 5 | > 1 | Total of cases follow-up (years) > 5 | > 1 |
|---|---|---|---|---|---|---|---|---|
| 80—100 | 63 } 110 | 85 } 150 | 69 4 } 60 4 | 63 9 } 64 1 | 43 } 72 | 48 } 81 | 106 } 182 | 133 } 234 |
| 70— 79 | 47 | 65 | 61.8 | 64.5 | 29 | 36 | 76 | 101 |
| 60— 69 | 40 } 162 | 68 } 274 | 56.3 } 63.5 | 61.8 } 68 3 | 31 } 94 | 42 } 127 | 71 } 256 | 110 } 401 |
| 40— 59 | 85 | 140 | 66 4 | 71 4 | 43 | 56 | 128 | 196 |
| 20— 39 | 34 | 60 | 65.4 | 69 6 | 18 | 26 | 52 | 86 |
| 0— 19 | 3 | 6 | 60.0 | 66.6 | 2 | 3 | 5 | 9 |
| Total | 272 | 424 | 62.1 | 66.8 | 166 | 211 | 438 | 65[illegible] |

*RR during the total treatment period.* Of the 720 cases, 635 were suitable for comparison of survival time and maximum RR during the entire treatment period Of the remaining 85 cases, 14 were excluded because no cytologic analyses were made after the first 14 days of treatment, 60 because satisfactory smears were not obtained after the 14th day and 11 because of unsatisfactory smears throughout the period of treatment.

The maximum readings of RR correlated to survival are recorded in Table 5 Survival is classified as in Table 4 as at least 5 years and at least 1 year Of the 438 patients with a 5-year follow-up, 182 had RR of 70 % or mor At the end of 5 years, 60 4 % of these patients were still alive the correspond ing figure among the patients with RR below 70 % being 63.5 %. Maximum RR during the whole period of treatment therefore provided no indication of the likelihood of cure

It was decided to investigate if RR might prove useful in predicting other clinical issues of the disease in view of the finding that RR had no apparent bearing on the final outcome in these cases of carcinoma of the cervix (cf. Tables 4 and 5) The correlation between maximum values for RR throughout the treatment period (Table 5) and radioincurability' and frequency of local recurrence pelvic and distal metastases, were therefore analyzed

### B Radiation response and radioincurability

Radioincurability was defined as failure of radiotherapy to control tumour growth within 6 months from institution of treatment. A patient with a radioincurable tumour theoretically should have a low RR.

Table 4

*Radiation response during the first 14 days of radiotherapy and survival*

| Radiation response ( ) | Number of patients alive at follow up (years) | | | | Percentages of patients alive t follow up (years) | | | | Number of deaths at follow-up (years) | | | | Total of patients t follow-up (years) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ( ) | >5 | | >1 | | >5 | | >1 | | >5 | | >1 | | >5 | | >1 | |
| 80—100 | 12 | 31 | 23 | 49 | 44 4 | 52.3 | 59 0 | 59 7 | 15 | 31 | 16 | 33 | 27 | 65 | 39 | 8. |
| 70— 79 | 22 | | 26 | | 57.9 | | 60 5 | | 16 | | 17 | | 38 | | 43 | |
| 60— 69 | 17 | 250 | 33 | 397 | 47 | 62.5 | 59 0 | 66.9 | 19 | 150 | 23 | 196 | 36 | 400 | 56 | 593 |
| 40— 59 | 49 | | 77 | | 53 4 | | 58,8 | | 43 | | 54 | | 92 | | 131 | |
| 20— 39 | 111 | | 145 | | 67 7 | | 66.8 | | 53 | | 72 | | 164 | | 217 | |
| 0— 19 | 73 | | 142 | | 67 6 | | 75 0 | | 35 | | 47 | | 108 | | 189 | |
| Total | 284 | | 446 | | 61 1 | | 65.9 | | 181 | | 229 | | 465 | | 673 | |

70 % of these 235 patients with poor RR 162 were alive and 73 were dead at the time of follow up of the 25 patients in whom good RR (70 % or more) was found at 12 to 14 days, 15 were alive and 10 were dead

The 5-year survival rate was thus 60 % in patients with good RR and 68 9 % in those with poor RR.

*RR during the first 14 days irrespective of treatment type* The survival rate was found not to be dependent upon RR in the selected material presented in Table 3 The correlation between survival and RR was therefore analyzed in the total series irrespective of whether the treatment had been along classical lines or otherwise The maximum RR during the first 14 days after initiation of treatment was recorded in each case

RR records for the first 14 days were suitable for analysis in 675 of the total 720 cases. The remaining 45 cases were excluded because the smears were considered to be unsatisfactory The highest percentage of cells with evidence of RR during this period was used for correlation with survival in each of the 675 cases. Table 4 gives this correlation in the cases with a 5-year or longer follow up and also in the cases with at least one year s observation.

RR was 70 or more in 65 of the cases observed for 5 years or more The survival rate was 52 3 % in this group with good RR in the 400 cases with RR below 70 % the 5 year survival was 62 5 %

These figures suggest that the RR at 12 to 14 days, or during the first 14 days of treatment has no prognostic significance A high RR thus did not imply a better 5-year cure rate than a low RR

Table 5

*Radiation response maximum during the whole treatment period and survival*

| Radiation response | Number of patients alive at follow-up (years) | | Percentages of patients alive at follow-up (years) | | Number of deaths at follow-up (years) | | Total of cases follow-up (years) | |
|---|---|---|---|---|---|---|---|---|
| ( ) | > 5 | > 1 | > 5 | > 1 | > 5 | > 1 | > 5 | > 1 |
| 80—100 | 63 } 110 | 83 } 150 | 69 4 } 60.4 | 63.9 } 64 1 | 43 } 72 | 48 } 84 | 106 } 182 | 133 } 234 |
| 70— 79 | 47 | 63 | 61.8 | 64.3 | 29 | 36 | 76 | 101 |
| 60— 69 | 40 } 162 | 68 } 274 | 56.3 } 63.3 | 61.8 } 68.3 | 31 } 94 | 42 } 127 | 71 } 256 | 110 } 401 |
| 40— 59 | 85 | 140 | 66.4 | 71 4 | 43 | 56 | 128 | 196 |
| 20— 39 | 34 | 60 | 65.4 | 69.8 | 18 | 26 | 52 | 86 |
| 0— 19 | 3 | 6 | 60.0 | 66.6 | 2 | 3 | 5 | 9 |
| Total | 272 | 424 | 62.1 | 66 8 | 166 | 211 | 438 | 635 |

*RR during the total treatment period.* Of the 720 cases 635 were suitable for comparison of survival time and maximum RR during the entire treatment period. Of the remaining 85 cases, 14 were excluded because no cytologic analyses were made after the first 14 days of treatment, 60 because satisfactory smears were not obtained after the 14th day and 11 because of unsatisfactory smears throughout the period of treatment.

The maximum readings of RR correlated to survival are recorded in Table 5 Survival is classified as in Table 4 as at least 5 years and at least 1 year Of the 438 patients with a 5-year follow up 182 had RR of 70 % or more. At the end of 5 years, 60 4 % of these patients were still alive the corresponding figure among the patients with RR below 70 % being 63.3 % Maximum RR during the whole period of treatment therefore provided no indication of the likelihood of cure.

It was decided to investigate if RR might prove useful in predicting other clinical issues of the disease in view of the finding that RR had no apparent bearing on the final outcome in these cases of carcinoma of the cervix (cf Tables 4 and 5) The correlation between maximum values for RR throughout the treatment period (Table 5) and radioincurability and frequency of local recurrence pelvic and distal metastases, were therefore analyzed.

## B Radiation response and radioincurability

Radioincurability was defined as failure of radiotherapy to control tumour growth within 6 months from institution of treatment. A patient with a radioincurable tumour theoretically should have a low RR.

Table 6

*Radiation response and local recurrence in carcinoma of the cervix*

| Clinical stage of tumour | Good response Total cases | Local recurrence Pre-menopausal | Post menopausal | % cases with recurrence | Poor response Total cases | Local recurrence Pre-menopausal | Post menopausal | cases with recurrence |
|---|---|---|---|---|---|---|---|---|
| I | 48 | 3 | 1 | 8.3 | 140 | 3 | 1 | 2.8 |
| II A | 68 | 1 | 2 | 4 4 | 139 | 8 | 6 | 10.1 |
| II B | 75 | 3 | 4 | 9.3 | 74 | 5 | 3 | 10.8 |
| III | 37 | — | 7 | 19 0 | 33 | 3 | — | 9 1 |
| IV | 6 | — | — | — | 8 | — | — | — |
| T tal | 234 | 7 | 14 | 9 0 | 394 | 19 | 10 | 7 4 |

Plus two cases of stage 0 carci oma, 4 with original diagnosis altered to carcinoma of terine body nd cervix and one case with diagnosis altered to vaginal carcinoma; all 7 cases had poor RR none had local recurrence.

Of the total of 720 cases in the series 135 were judged to be radioincurable The corresponding figure in the 635 cases in which the maximum RR was determined (Table 5) was 115 In 53 of these 115 cases the maximum RR was 70 % or more and in 62 cases the maximum readings were *less than* 70 % Among the 520 cases clinically regarded as radiocurable, and having measurable maximum RR 339 had low RR The respective frequencies of low maximum RR were therefore 53 9 % in the radioincurable cases and 65 2 % in the radiocurable cases.

A similar trend was found when clinically assessed radioincurability was compared with RR among the total 635 cases in Table 5 Of the 234 cases with good RR 22 6 % (53 cases) were judged to be radioincurable but only 15 5 % (62 cases) of the 401 with poor RR

It therefore seemed that poor RR did not necessarily entail radioincurability and that the measurement of the RR is not a suitable test for predicting radioincurability in individual cases of carcinoma of the cervix.

### *C Radiation response and local recurrence*

HULTBERG (1944) considered the reappearance of carcinoma within the uterus or the upper third of the vagina after four months of apparent local primary healing and after two negative clinical examinations as a local re-

currence The four-month-period has been extended to six months in this communication.

Fifty-four of the total 720 cases in the present series had local recurrence The corresponding frequency among the 635 cases in which the maximum RR could be determined was 50

The frequency of local recurrence in relation to RR is shown in Table 6. Nine per cent of the 234 cases with good RR, and 7 4 % of the 394 with poor RR, had a local recurrence When only the cases with 5-year survival were considered, the results were similar — local recurrence in 8.8 % of the cases with good RR, and in 9.5 % of those with poor RR.

There was thus no obvious association between RR and frequency of carcinoma recurrence in loco.

*D Radiation response and metastases*

Metastases of the tumour as judged by clinical examination, occurred in 142 of the total 720 cases and in 125 of the 635 cases in which maximum RR was estimated In 44 (35.2 %) of these cases with metastases, the RR was good, and in 81 cases (64.8 %) it was poor

When the frequency of metastases was compared with measurable maximum RR in the total series, it was found that metastatic spread occurred in 18.8 % (44 cases) of the 234 cases with good RR, and in 20.2 % (81 cases) of the 401 with poor RR. Analysis of these cases according to whether the spread was apparently purely intrapelvic (46 cases) or apparently purely distal (26 cases) revealed no noteworthy deviation from the mentioned frequencies.

RR therefore seemed to have no clear prognostic significance as regards metastatic dissemination of the tumours.

*E. Radiation response and radiation injuries*

Untoward reactions to radiotherapy were classified as grade I, II or III (Kottmeier & Gray 1957) Grade I injuries consisted only of mild mainly subjective manifestations and these reactions were not considered in the present connection.

Grade II injuries were those accompanied by moderately severe objective changes, such as areas of necrosis, ulcers or moderate stenosis, or those accompanied by protracted bleeding or pain. Such injury occurred in 64 cases of the total 720 and in 58 of the 635 in which maximum RR was estimated. Theoretically one might expect RR to be high in cases with radiation injury (Kjellgren 1958) In 37 of the 58 cases, however the maximum RR was

Table 6

*Radiation response and local recurrence in carcinoma of the cervix*

| Clinical stage of tumour | Good response | | | | Poor response | | | |
|---|---|---|---|---|---|---|---|---|
| | Total cases | Local recurrence | | | Total cases | Local recurrence | | |
| | | Pre-menopausal | Post menopausal | % cases with recurrence | | Pre-menopausal | Post menopausal | % cases with recurrence |
| I | 48 | 3 | 1 | 8.3 | 140 | 3 | 1 | 2.8 |
| II A | 68 | 1 | 2 | 4.4 | 139 | 8 | 6 | 10.1 |
| II B | 75 | 3 | 4 | 9.3 | 71 | 5 | 3 | 10.8 |
| III | 37 | — | 7 | 19.0 | 33 | 3 | — | 9.1 |
| IV | 6 | — | — | — | 8 | — | — | — |
| Total | 234 | 7 | 14 | 9.0 | 391 | 19 | 10 | 7.4 |

Plus two cases of stage 0 carcinoma, 4 with original diagnosis altered to carcinoma of uterine body and cervix and one case with diagnosis altered to vaginal carcinoma; all 7 cases had poor RR, none had local recurrence.

Of the total of 720 cases in the series, 135 were judged to be radioincurable. The corresponding figure in the 635 cases in which the maximum RR was determined (Table 5) was 115. In 53 of these 115 cases, the maximum RR was 70 % or more, and in 62 cases the maximum readings were less than 70 %. Among the 520 cases clinically regarded as radiocurable, and having measurable maximum RR, 339 had low RR. The respective frequencies of low maximum RR were therefore 53.9 % in the radioincurable cases and 65.2 % in the radiocurable cases.

A similar trend was found when clinically assessed radioincurability was compared with RR among the total 635 cases in Table 5. Of the 234 cases with good RR, 22.6 % (53 cases) were judged to be radioincurable, but only 15.5 % (62 cases) of the 401 with poor RR.

It therefore seemed that poor RR did not necessarily entail radioincurability, and that the measurement of the RR is not a suitable test for predicting radioincurability in individual cases of carcinoma of the cervix.

*C. Radiation response and local recurrence*

Hultberg (1944) considered the reappearance of carcinoma within the uterus or the upper third of the vagina after four months of apparent local primary healing and after two negative clinical examinations as a local re-

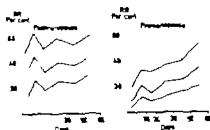


Fig. 1 Distribution of medians and quartiles of mean radiation response' in 230 premenopausal and 142 postmenopausal cases of carcinoma of the cervix treated according to the standard 'Stockholm method and followed up for 5 years.

not provide a true reflection of individual RR. An attempt was therefore made by detailed analysis to determine mean RR in individual cases and to study the significance of mean RR for survival.

*I Calculation of mean radiation response*

The statistical analysis comprised only cases in which the standard 'Stockholm treatment had been given. The intention was to make the clinical material where radiotherapy was concerned as homogeneous as possible. As the authors wished to compare mean RR with survival, the case series was further limited to those in which the observation period was at least five years. These requirements were satisfied by 372 cases (230 premenopausal and 142 postmenopausal)

The treatment (Ra I + Ra II + roentgen rays) lasted for 60 days or more and was divided into six periods after the application of Ra I. These were as follows ≮ 8 days 8—16 16—24 24—38, 38—52 and 52—66 days The first 8 days were considered to comprise the period prior to expected maximum RR. The 8—16 day period included the period of maximum RR, which is regarded as being 12 to 14 days after initiation of treatment (Graham 1958, Davis et coll. 1960) The third period marked the commencement of Ra II. The 24—38 day period was expected to show the effect of Ra II application on RR, and the 38—52 and 52—66 day periods to indicate the influence of roentgen irradiation.

Of the 372 patients, 116 had one or more determinations of RR in all of the six periods in the other 256 RR readings were lacking in one or more of these periods.

As a preliminary step in calculating individual mean RR for the total period of treatment, individual means of RR during the six mentioned intervals were calculated according to the formula

$$\widetilde{RR} = \sum RR_{\psi}/n$$

poor and in 21 cases (36 2 %) it was good The latter frequency was remarkably similar to the frequency of good RR in the cases with neither grade II nor grade III injury (207 of 564 cases = 36 7 %)

Of the total 234 cases with good maximum RR 21 (9 %) had grade II radiation injury The corresponding figures among the 401 cases with poor maximum RR were 37 (9 2 %)

Grade III radiation injury (radiation fistulas and rectal stenoses severe enough to require a colostomy) occurred in 20 of the total 720 cases in the series and in 13 of the 635 cases with an estimated maximum RR. Six of these 13 cases had good and 7 had poor maximum RR Although the cases were few the trend resembled that in the cases with grade II injury viz. maximum RR was not a reliable guide to the individuals sensitivity to ionizing radiation

*F Radiation response and surgical castration or supplemental medication*

The possibility of modifying individual sensitivity to radiation by the administration of steroids and heterologous proteins was discussed by GRAHAM & GRAHAM in 1949 The influence of alpha tocopherol and androgenic substances on the RR was dealt with in later reports (GRAHAM et coll 1950 1952, 1953) The experimental findings suggested that the agents mentioned could modify the RR

The forty two cases in which bilateral salpingo-oophorectomy had been performed and the 60 cases in which alpha tocopherol or androgenic substances had been administered were reviewed in order to test this hypothesis in the series Sixty-eight of these 102 cases had 5 years or more of follow up. Maximum RR readings were available in 89 cases and were classified as good in 30 cases (33 7 %) a similar value (37 4 %) was found in 546 cases without supplemental hormonal therapy

It was therefore concluded that surgical castration or supplemental medication did not modify the RR in the cases. This conclusion is in agreement with recent observations (KJELLGREN 1962 GRAHAM & GRAHAM 1962)

## Statistical analysis of radiation response in cases with standard treatment

The RR in individual cases is presented in Tables 3 to 5 as maximum readings in accordance with general practice Since however it was found that maximum RR had no apparent bearing on the prognosis in carcinoma of the cervix the possibility was considered that such maximum values might

Tables 8 and 9

*Premenopausal cases classified according to radiation response*

Table 8 at < 8 days ($\overline{Y}$) and at 24—38 days ($\overline{Y}$)

| | Low response $\overline{Y} < 2.5$ | High response $\overline{Y} > 2.5$ | Total |
|---|---|---|---|
| Low response $\overline{Y}_{24} < 2.5$ | 45 | 30 | 75 |
| High response $\overline{Y}_{24} > 2.5$ | 34 | 47 | 81 |
| Total | 79 | 77 | 156 |

$\chi^2 = 3.06$ d.f. = 1 $\chi^2_{0.05} = 3.84$

Table 9 at 24—38 days ($\overline{Y}_{24}$) and at 52—66 days ($\overline{Y}_{52}$)

| | Low response $\overline{Y}_{24} < 2.5$ | High response $\overline{Y}_{24} > 2.5$ | Total |
|---|---|---|---|
| Low response $\overline{Y}_{52} < 2.5$ | 64 | 33 | 97 |
| High response $\overline{Y}_{52} > 2.5$ | 34 | 56 | 90 |
| Total | 98 | 89 | 187 |

$\chi^2 = 14.89$ d.f. = 1 $\chi^2_{0.05} = 3.84$

permit comparisons between RR measured during the various time intervals. As mentioned, RR was obtained during all six intervals in 116 cases. The number of intervals during which RR readings were made in the remainder of the series was five in 154 cases, four in 71 cases, three in 35 cases, two in 10 cases, and one in 6 cases.

If comparisons between patients were based upon arithmetical means of RR at different times, the results might well be misleading because, as shown in Fig 1 there was a time trend in the values. For example, if in one premenopausal patient the RR was calculated at < 8 8—16 and 16—24 days, and was 22 % on all occasions, while another premenopausal patient was studied at 24—38, 38—52 and 52—66 days and also had a RR of 22 % on all occasions, both would have a mean RR of 22 %. However in the first the response is high in relation to the mean for the total of premenopausal patients during the first three intervals (Fig 1) but the second patient had a relatively low response in the last three intervals. If however the mean RR is calculated as

Table 7

*Calculation of mean radiation response ($\overline{Y}$) for total treatment period in a premenopausal case*

| | Time in days | | | | | |
|---|---|---|---|---|---|---|
| | < 8 | 8—16 | 16—24 | 24—38 | 38—52 | 52—66 |
| Measurement of response $RR_{ij}$ (%) | 13 17 | 39 32 | 47 | 45 | — | 55. 5. |
| Class number $Y_{ij}$ | 3 3 | 4 3 | 4 | 4 | — | 4 3 |
| Mean class number $\overline{Y}_i$ | 3.0 | 3.5 | 4.0 | 4.0 | — | 3.5 |

$$RR_{\overline{Y}} = \frac{3.0 + 3.5 + 4.0 + 4.0 + 3.5}{5} = 3.6$$

where i indicates the interval in which RR was determined, j the order of the determination and n the number of determinations made during interval i. Thus $RR_{..}$ denotes a value calculated during the 8—16 day interval and is the third determination in the case.

Medians and quartiles of these means were then computed for each interval with separate calculations for premenopausal and postmenopausal patients (Fig. 1). In one fourth of the premenopausal patients the response at < 8 days ($\overline{RR}$) was higher than 20 % and that the same proportion of the group had values between 20 % and 9 %, between 9 % and 4 and below 4 %.

Mean RR during the total period of radiotherapy ($RR_{\overline{Y}}$) could now be deduced for individual patients with the aid of the calculated medians and quartiles. Once more the premenopausal group and the postmenopausal group were kept apart. This calculation of $RR_{\overline{Y}}$ is illustrated in Table 7.

Each $RR_{ij}$ value was transformed to a class number ($Y_{ij}$). If $RR_{ij}$ was below the lower quartile at the time interval i, $Y_{ij} = 1$. If $RR_{ij}$ lay between the lower quartile and the median, $Y_{ij} = 2$. Between the median and the upper quartile $Y_{ij} = 3$, and $RR_{ij}$ higher than the upper quartile gave $Y_{ij} = 4$. The mean class number ($\overline{Y}_i$) was calculated according to the formula for each interval

$$\overline{Y}_i = \sum_j Y_{ij}/n$$

Finally the mean RR for the total treatment period in individual cases ($RR_{\overline{Y}}$) was expressed as the arithmetical mean of the values of $\overline{Y}$.

The purpose of the transformation of RR values to class numbers was to

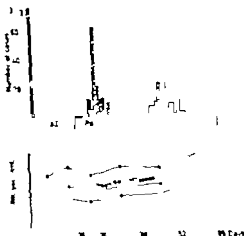


Fig. 2. Mean radiation response in 137 cases given standard Stockholm treatment for carcinoma of the cervix and having one or more readings of RR in each of the six periods after application of Ra I.
△ = all cases (average reading at < 8 days = 17.8 %)
○ = 52 cases with mean RR at < 8 days above 17.8 %
● = 85 cases with mean RR at < 8 days below 17.8 %
Radiotherapy in the 137 cases is also illustrated.

treatment and having one or more readings of RR in each of the six intervals. The results are presented in Fig. 2, where the triangles denote the arithmetical mean of RR for the total series at each interval. At < 8 days, this total mean was 17.8 %. The individual values lay above the mean in 52 cases and below the mean in 85 cases. In the 52 cases (open circles) the initially higher than mean values were maintained throughout irradiation, as were the initially lower than mean values (filled circles) in the 85 cases. The curves for the two groups run parallel and, like those in Fig. 1, have a tendency to rise during the period of radiotherapy.

*II. Significance of mean radiation response for survival*

In table 12, the mortality in the premenopausal patients is recorded in relation to stage of tumour and mean radiation response ($RR_{\bar{T}}$). Dependence of mortality upon $RR_{\bar{T}}$ was investigated for each clinical stage but no significant correlation was found. When all tumour stages were collectively considered, however, the mortality among the patients with high $RR_{\bar{T}}$ was found to be greater than in those with low $RR_{\bar{T}}$.

Possible explanations of this association of high $RR_{\bar{T}}$ and mortality were an intrinsic relationship between the two factors, or that $RR_{\bar{T}}$ tended to be high when the tumours were clinically advanced and thus as such entailed higher mortality rates. As may be seen from Table 13, the combinations of low $RR_{\bar{T}}$ with early tumour stage and high $RR_{\bar{T}}$ with advanced tumour stage were much more frequent than might have been expected if there had been no association between tumour stage and $RR_{\bar{T}}$. Accordingly, the fre

**Tables 10 and 11**

*Postmenopausal cases classified according to radiation response*

**Table 10** *at < 8 days ($\overline{Y}_8$) and at 24—38 days ($\overline{Y}_{31}$)*

| | Low response $\overline{Y}_8 < 2.5$ | High response $\overline{Y}_8 > 2.5$ | Total |
|---|---|---|---|
| Low response $\overline{Y}_{31} < 2.5$ | 30 | 7 | 37 |
| High response $\overline{Y}_{31} > 2.5$ | 10 | 27 | 37 |
| Total | 40 | 34 | 74 |

$\chi^2 = 21.77$ d.f. $= 1$ $\chi^2_{0.95} = 3.84$

**Table 11** *at 24—38 days ($\overline{Y}_{31}$) and at 52—66 days ($\overline{Y}_{59}$)*

| | Low response $\overline{Y}_{31} < 2.5$ | High response $\overline{Y}_{31} > 2.5$ | Total |
|---|---|---|---|
| Low response $\overline{Y}_{59} < 2.5$ | 33 | 17 | 50 |
| High response $\overline{Y}_{59} > 2.5$ | 17 | 37 | 54 |
| Total | 50 | 54 | 104 |

$\chi^2 = 12.39$ d.f. $= 1$ $\chi^2_{0.95} = 3.84$

in Table 7 these factors are taken into account and the respective values will be $(4 + 3 + 3)/3 = 3.3$ and $(2 + 2 + 2)/3 = 2.0$

Because RR was dependent upon time (Fig. 1) it could be expected that a case with high RR during one interval would show high RR also in subsequent intervals. A comparison is made in Table 8 between values at $\leq 8$ and at 24—38 days in the 156 patients who were studied during both intervals. High RR is defined as mean class value $\geq 2.5$ and low RR as $< 2.5$. The hypothesis that there is no association between RR in the two intervals may be rejected since $\chi^2$ is higher than 3.84. Low $\overline{Y}_8$ low $\overline{Y}_{31}$ and high $\overline{Y}_8$ high $\overline{Y}_{31}$, were the most frequently occurring combinations. The same trend is evident in Tables 9, 10 and 11. It may therefore be concluded that the patients tended to maintain similar mean class values throughout the period of radiotherapy.

This assumption was further tested by analysis of the 137 cases (116 of them with follow up for 5 years or more) given the standard Stockholm

Table 14

*Mortality in relation to radiation response and clinical tumour stage in postmenopausal cases*

| Mean radiation response (RRV) | Stage I | | Stage II-A | | Stage II-B | | Stage III | | Stage IV | | All cases | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of cases | Mortality (%) | No. of cases | Mortality (%) | No. of cases | Mortality (%) | No. of cases | Mortality (%) | No. of cases | Mortality (%) | No. of cases | Mortality (%) |
| 1.00—1.59 | 5 | 0 | 7 | 14 | 5 | 40 | 2 | 50 | — | | 19 | 21 |
| 1.60—2.19 | 13 | 31 | 18 | 33 | 6 | 33 | 1 | 100 | — | | 38 | 34 |
| 2.20—2.79 | 5 | 0 | 12 | 8 | 8 | 13 | 4 | 0 | — | | 29 | 14 |
| 2.80—3.39 | 8 | 0 | 13 | 38 | 5 | 40 | 2 | 100 | 1 | 0 | 29 | 31 |
| 3.40—4.00 | 5 | 0 | 9 | 11 | 8 | 75 | 4 | 75 | 1 | 100 | 27 | 41 |
| Total | 36 | 11 | 59 | 24 | 32 | 47 | 13 | 54 | 2 | 50 | 142 | 29 |

tumour stage was not so marked as in the premenopausal group Thus, although the postmenopausal patients showed some trend towards higher $RR_V$ with advancing clinical stage of the tumours (Table 15) the hypothesis of no association between radiation response and tumour stage could not be rejected in this group

No relationship could therefore be proved between mean radiation response and mortality in premenopausal or in postmenopausal patients with carcinoma of the cervix. On the other hand, an association between clinical tumour stage and mean radiation response was statistically demonstrated in the premenopausal patients. If tumour stage is not taken into account, such an association may give a false impression of higher mortality in patients with high mean radiation response.

Table 15

*Observed and predicted distribution according to radiation response and clinical tumour stage in postmenopausal cases*

| Mean radiation response | Stages I + II A | | Stages II B + III + IV | | Total |
|---|---|---|---|---|---|
| | No. of cases | | No. of cases | | |
| | Observed | Predicted | Observed | Predicted | |
| 1.00—2.19 | 43 | 38.13 | 14 | 18.87 | 57 |
| 2.20—4.00 | 52 | 56.87 | 33 | 28.13 | 85 |
| Total | 95 | | 47 | | 142 |

$\chi^2 = 3.13$ d f = 1 $\chi^2_{0.05} = 3.84$

**Table 12**

*Mortality in relation to radiation response and clinical tumour stage in premenopausal cases*

| Mean radiation response ($RR_{\bar{y}}$) | Stage I | | Stage II A | | Stage II B | | Stage III | | Stage IV | | All cases | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of cases | Mortality (%) | No. of cases | Mortality (%) | No. of cases | Mortality (%) | No. of cases | Mortality (%) | No. of cases | Mortality (%) | No. of cases | Mortality (%) |
| 1.00—1.59 | 19 | 16 | 8 | 38 | 3 | 67 | — | | — | | 30 | 27 |
| 1.60—2.19 | 29 | 3 | 24 | 33 | 11 | 55 | 3 | 100 | — | | 67 | 27 |
| 2.20—2.79 | 20 | 5 | 22 | 41 | 13 | 31 | — | | 2 | 100 | 57 | 28 |
| 2.80—3.39 | 10 | 20 | 20 | 21 | 7 | 29 | 3 | 100 | — | | 40 | 28 |
| 3.40—4.00 | 6 | 33 | 11 | 36 | 14 | 50 | 5 | 80 | — | | 36 | 47 |
| Total | 84 | 11 | 85 | 33 | 48 | 44 | 11 | 91 | 2 | 100 | 230 | 30 |

quency of high $RR_{\bar{y}}$ combined with early stage and that of low $RR_{\bar{y}}$ with advanced stage were below the predicted values. The statistically significant correlation between $RR_{\bar{y}}$ and tumour stage could have explained the association observed between $RR_{\bar{y}}$ and mortality.

The postmenopausal patients are classified in Table 14 according to clinical stage of tumours, radiation response and mortality. Again, no correlation was found between $RR_{\bar{y}}$ and mortality when the tumour stages were separately analyzed. As in the premenopausal patients (Table 12), the mortality rate was higher among those with high $RR_{\bar{y}}$ when all tumour stages were collectively considered. This tendency was less clear in the postmenopausal patients, however, possibly because the association between high $RR_{\bar{y}}$ and advanced

**Table 13**

*Observed and predicted distribution according to radiation response and clinical tumour stage in premenopausal cases*

| Mean radiation response | Stage I | | Stage II A | | Stages II B+III+IV | | Total |
|---|---|---|---|---|---|---|---|
| | No. of cases | | No. of cases | | No. of cases | | |
| | Observed | Predicted | Observed | Predicted | Observed | Predicted | |
| 1.00—2.19 | 48 | 35.43 | 32 | 35.85 | 17 | 25.72 | 97 |
| 2.20—4.00 | 36 | 48.57 | 53 | 49.15 | 44 | 35.28 | 133 |
| Total | 84 | | 85 | | 61 | | 230 |

$\chi^2 = 13.54$ d.f. $= 2$ $\chi^2_{0.95} = 5.99$

MANN (1945) devised a test in which the radiosensitivity of carcinoma of the cervix was estimated by means of serial biopsies. He reported that the salvage rate was improved by about 14 % when cases recognized as radioresistant were surgically treated after irradiation (GLUCKSMANN 1958). This method has not been systematically studied at Radiumhemmet as it was feared that repeated biopsy during radiotherapy might interfere with healing of the tumours (KOTTMEIER 1959).

The problem of determining radiosensitivity of human tumours has recently been approached by the less traumatic method of aspiration biopsy. Tumours were aspirated with a fine (22 gauge) needle at various intervals during the course of irradiation and were submitted to morphologic and biologic studies (JOHANSSON & ZAJICEK 1963). Primary carcinomas of the uterine cervix (GREGUREVIC & ZAJICEK 1962, unpublished data) and the breast, malignant metastases to lymph nodes and various primary and metastatic sarcomas were investigated in this way.

It was observed that tumours which clinically are regarded as radiosensitive — according to MERRILL (1958) a tumour is radiosensitive when it shrinks rapidly and heals under the direct influence of irradiation — such as lymphoblastic lymphomas, seminomas, undifferentiated carcinomas and sarcomas, displayed in smear preparations or in suspensions a marked decrease of mutual adhesiveness and behaved as individually free cells. It was therefore suggested that such clinically assessed radiosensitivity might be partly due to rapid mobilization and disappearance of free tumour cells during irradiation (JOHANSSON & ZAJICEK 1963). The number and nature of tumour cells mobilized from irradiated areas is difficult to evaluate, however, and analysis of tumour cell populations during radiotherapy is of questionable value for predicting the biologic response of the tumour to treatment.

The Grahams presented a novel approach to the problem by suggesting that radiocurability could be predicted from the study of normal squamous cells exfoliated into the vagina prior to irradiation (sensitization response) or during irradiation (radiation response). Much of the attractiveness of these methods lay in their simplicity and non-surgical nature. Clinical trials in various centres have resulted in an impressive volume of literature on sensitization response (SR) and radiation response (RR).

Figures from the available literature dealing with SR and survival rates in carcinoma of the cervix are presented in Table 17. Only a few of these investigations corroborated the Grahams' findings that good SR was associated with considerably higher survival rates after radiotherapy than poor SR. The strongest support was provided by OSTBERG & DARGIE from this centre in 1956. They stated that of 48 patients with good SR, 91.7 % were

Table 16

*Relationship between sensitization response and radiation response*

| | Premenopausal | | | Postmenopausal | | |
|---|---|---|---|---|---|---|
| | Good RR | Poor RR | Total | Good RR | Poor RR | Total |
| Good SR | 13 | 7 | 20 | 66 | 30 | 96 |
| Poor SR | 94 | 216 | 310 | 44 | 85 | 129 |
| Total | 107 | 253 | 360 | 110 | 115 | 225 |

## Relationship between SR and RR

Both RR and SR were estimated in 585 cases. Table 16 indicates that in 410 (70 %) of these a good SR coexisted with a good RR or a poor SR with a poor RR. Graham's report of 1953 stated that 79.1 % of the patients had good SR with good RR or poor SR with poor RR. It appears from the table that this relationship was found in the postmenopausal as well as in the premenopausal group. Thus, of 20 premenopausal and 66 postmenopausal patients with good SR, 65 % and 69 % respectively had good RR.

The frequency of good SR differed in the two groups however. Whereas only 5.5 % of the 360 premenopausal patients had good SR, the frequency of good SR in the postmenopausal patients was 42.7 % (Table 16). Furthermore, of the 116 patients with good SR in table 16, 82.7 % were postmenopausal. It would therefore seem that the SR phenomenon most probably is hormone dependent. This suggestion has already been advanced by ÖSTBERG & DARGIS (1956).

## Discussion

Although selected cases of carcinoma of the uterine cervix may be successfully treated by radical surgery, the treatment of choice is generally considered to be irradiation. The possible influence of various factors on the results of radiotherapy has been widely discussed. Such factors include the patient's general health, histologic type of the tumour, local and/or distant spread of malignancy when treatment is initiated and immunologic response of the host to the neoplasm.

The question of primarily radioresistant tumours has been widely debated in recent years and several methods have been evolved for estimating sensitivity to irradiation in carcinoma of the cervix. The literature on the subject was reviewed by MERRILL (1958), DAVIS (1960) and DARGIS (1962). GLUCKS-

Table 18

*Radiation response and survival in some reports in the literature*

| Authors | No. of cases | Clinical stages | Follow-up in years | Good/Poor RR | Alive Good RR | Poor RR |
|---|---|---|---|---|---|---|
| Graham (1957) | 130 | I—IV | 5 | 62/68 | 40 (65 %) | 7 (10 %) |
| Gompel (1958) | 46 | I—IV | 5 | 34/12 | 26 (77 %) | 5 (42 %) |
| Kjellgren (1958) | 241 | I—IV | 5 | 115/126 | 85 (74 %) | 46 (37 %) |
| Mussey (1958) | 145 | 0—IV | 4—6 | 72/73 | 67 (92 %) | 23 (31 %) |
| Jones et coll. (1959 | 68 | I—II | 2 | 27/41 | 17 (63 %) | 27 (66 %) |
| Ags w et coll. (1960) | 107 | I—III | 5 | 76/31 | 53 (70 %) | 8 (26 %) |
| Mitchell (1961) | 99 | 0—IV | 2—4 | 82/17 | 62 (76 %) | 8 (47 %) |
| Smith (1961) | 272 | I—II | 5 | 223/49 | 122 (55 *) | 20 (41 %) |
| Grattarola & Luciani (1962) | 73 | I—III | 3 | 42/31 | 27 (64 %) | 9 (29 %) |
| Zeek & Morris (1962) | 146 | I—IV | 3—8 | 105/41 | 66 (63 %) | 23 (58 % |
| Fenner & Garin (1963) | 50 |  | 3—5 | 42/8 | 6 (14 %) | 2 (23 %) |
| Moore et coll. (1963) | 87 | I—IV | 1—5 | 57/30 | 44 (77 %) | 8 (27 %) |
| Kalbano & Kanam (1964) | 132 | I—IV | 2 1/2—6 | 36/96 | 31 (86 *) | 71 (74 %) |
| Present series (1964) |  |  |  |  |  |  |
| a) Total material | 635 | I—IV | 1—8 | 234/401 | 150 (64 %) | 274 (61 %) |
| b) 5-year follow-up | 438 | I—IV | 5—8 | 182/256 | 110 (60 %) | 162 (63 *) |

* Non-cervical cancers of the female genital tract

** Cure rate

between maximum RR values and survival (Table 5) nor was there any association between individual means of RR during the total treatment period and survival rates (Tables 12 and 14)

Several factors invited consideration in the search for an explanation of the variation in the RR as an index of curability in radiologically treated carcinoma of the cervix (cf Table 18)

*1 Size of material.* A small series of cases tends, of course to give unreliable results. As an example may be cited an earlier report from this centre (Kotte 1954) which was based on only 50 cases of carcinoma of the cervix and indicated association between poor RR and frequency of recurrence This finding was not confirmed in the present analysis of 635 cases. On the other hand, correlation between good RR and high survival rates, and vice versa, have been statistically demonstrated in well-documented case series. The work of Kjellgren (1958) merits special attention he found that 73.9 % of 115 patients

**Table 17**

*Sensitization response and survival in some reports in the literature*

| Authors | | No. of cases | Follow-up (years) | Alive Good SR | Poor SR |
|---|---|---|---|---|---|
| Östberg & Darcis | (1956) | 200 | 2—4 | 41 (92 %) | 82 (54 ) |
| Lanier & Wikle | (1959) | 96 | 5—8 | 15 (58 ) | 33 (48 ) |
| Coleman et coll. | (1960) | 133 | 5 | 18 (67 %) | 55 (52 ) |
| Graham & Graham | (1960) | 147 | 5 | 37 (69 ) | 17 (18 ) |
| Merrill | (1961) | 101 | —4 | 28 (55 ) | 36 (72 ) |
| Siter | (1961) | 149 | 5 | 26 (62 ) | 57 (53 %) |
| Zerne & Morris | (1962) | 127 | 3—8 | 29 (57 ) | 48 (63 ) |
| Present series | (1964) | 449 | 5—8 | 54 (57 ) | 244 (63 ) |

alive after 2 to 4 years of observation as compared with 53.9 % of 152 patients with poor SR. In the present study 449 patients in whom SR could be compared with survival were followed up for 5 to 8 years (Table 2). The staff responsible for the SR readings were the same as in the investigation described by Östberg & Darcis but a higher survival rate among the patients with good SR was not recorded; in fact, these patients had a somewhat poorer prognosis (cf. Table 2).

Our observations thus indicated that SR had no bearing on survival in carcinoma of the cervix treated by irradiation. The study confirmed previous reports in another respect, viz. that good SR seemed to be associated with decreased ovarian function (Östberg & Darcis 1956, Herman et coll. 1959, Zerne & Morris 1962). Table 16 reveals that good SR was more frequently found among postmenopausal than among premenopausal patients. The postmenopausal state thus seemed in general to be a prerequisite for a sensitization response in non-malignant exfoliated vaginal cells. Some connection was also established between SR and the clinical stage of the cervical carcinomas. Good SR was more frequent in advanced stages than in early stages. The reason for this difference is obscure.

Even greater than the clinical interest aroused by the Grahams' work on SR was that evoked by the prognostic and general radiobiologic implications of RR. Available published reports on RR and survival are summarized in Table 18. It is seen that the majority of these are in agreement with the Grahams' observations that good RR is associated with better survival rates than is poor RR. Some of the writers, however, were unable to substantiate the Grahams' findings (Jones et coll. 1959, Feiner & Garin 1963). A 5 to 8 year follow up of 438 cases of the present series similarly revealed no relationship

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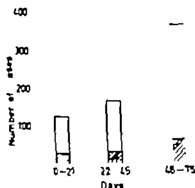



Fig. 3. Occurrence of maximum radiation response during radiotherapy in 634 cases. The unfilled parts of the columns indicate cases receiving standard Stockholm treatment.

agreement with Merrill's report. Tables 12 and 14 indicate that higher RR readings were found in advanced tumour stages (II B—IV) than in early stages (I, II A)

3 *Progression of radiotherapy* Graham (1958) reported that the cellular response in carcinoma of the cervix was related to the amount of radiation received at the cervix this was measured in tumour dose. Kjellgren (1962) on the other hand, could demonstrate no significant relationship between radiation dosage delivered to the bladder (measured in R/h) or the vagina (measured in mg/h) and the degree of RR in vaginal smears. There was, however a statistically significant correlation between the radiation dosage received at the rectum and RR.

The radiation dosage was not taken into consideration in the present series of cases. It was felt that the true dosage acting on the vaginal epithelium would be inaccurately assessed by indirect conclusions based on radiation measured in tumour doses or in mg of R/h. It is therefore not known to what extent fluctuations of RR values in individual patients were dependent upon variations in radiation dosage. It was however noted that RR was influenced by the duration of treatment. Fig 3 shows that, irrespective of the mode of initiating radiotherapy maximum RR occurred after 46 to 75 days in more than half the number of patients. The influence of progression of radiotherapy on RR is further illustrated in Fig 2, which presents mean RR in various groups during the course of radiotherapy

The various circumstances that might have influenced conclusions concerning relationship between RR and tumour curability having been considered, no obvious explanation of the differences between the reports summarized in Table 18 can be offered. Of the factors discussed under the sub-

with good RR but only 36.5 % of 126 patients with poor RR survived for 5 years.

*II. Reading of RR.* Differing interpretations of the cytologic changes could have been responsible for the discrepancies between the present other investigators observations and those made by KJELLGREN and the GRAHAMS. This possibility could be disregarded, however, as in many investigations the staff who read the smears had received training at the Grahams laboratory (AGNEW et coll. 1960, SHIER 1961, MERRILL 1961, KJELLGREN 1958, present investigation).

*III. Choice of RR limits.* In demarcating good from poor RR some workers used the classification suggested by GRAHAM in 1955, i.e. > 75 % for good RR and < 60 % for poor RR. Others followed the Grahams subsequent (1957) recommendation of > 70 % for good RR and < 69 % for poor RR. This was the definition employed by us. A number of writers chose other criteria (KJELLGREN 1958, MERRILL 1962, MOORE 1963). That arbitrary choice in this respect may help to explain differences in results is conceivable. Tables 4 and 5 indicate, however, that in the present study no correlation was discernible between maximum RR and survival even if demarcations other than 70 % had been selected. Tables 12 and 14 disclose that this absence of correlation also existed when different levels of *mean* RR were compared with survival.

*IV. Dependence of RR on various factors.* The possibility remains that intrinsic differences in RR may have existed between some of the case series in the literature. The factors that promote radiation response in the vaginal epithelium must be taken into account in considering this theory.

1. *Hormonal condition.* The influence of the patient's hormonal condition on RR has been reported in the literature. KJELLGREN (1958) and MERRILL (1962) found greater frequency of good RR among postmenopausal than among premenopausal patients. This observation was decisively corroborated in the present study. When radiotherapy was initiated, RR was higher in the postmenopausal than in the premenopausal patients (Fig. 1), SR behaving similarly to RR. As the morphologic details are to some extent parallel in both phenomena, it is possible that the higher RR in postmenopausal patients is in some degree influenced by an antecedent high SR.

2. *Clinical tumour stage.* That the RR may be influenced by the clinical stage of the tumour was suggested by MERRILL in 1961. Our observations are in

## ZUSAMMENFASSUNG

Die Empfindlichkeitsreaktion (SR) und die Bestrahlungsreaktion (RR) wurden bei 720 Patienten studiert, die für Cervixcancer behandelt wurden. SR hatte keine prognostische Signifikanz, war aber deutlicher in Menopause als vorher Auch die maximale und durchschnittliche Werte der Bestrahlungsreaktion zeigten keine Beziehung zum Krankheitsverlauf. Die Autoren besprechen die zahlreichen Faktoren die die Bestrahlungsreaktion (RR) beeinflussen.



## RÉSUMÉ

La réaction de sensibilisation (SR) et la réaction aux radiations (RR) ont été étudiées chez 720 malades traitées pour cancer d col d l'utérus On constaté que la SR n pas de signification pronostique mais qu elle est plus forte chez les malades postménopausiques que chez les préménopausiques. On constaté aussi que les valeurs maximales et moyennes de la RR sont sans relation avec l évolution de cette affection. Les auteurs examinent les nombreux facteurs qui influent la éaction aux radiations (RR)


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headings I to IV however it would seem that the apparent dependence of RR on the hormonal condition, on the clinical tumour stage and especially on the progression of radiotherapy may contribute to discrepancies in results if RR values are uncritically correlated to tumour curability

Clinical experience has shown that radiocurability in carcinoma of the cervix tends to be associated with various circumstances when treatment is begun — *the patient's general health histologic type and clinical stage of the tumour* immunologic host response and radiosensitivity of the neoplasm. If all these factors were known in the individual patient accurate prediction of the outcome would presumably be feasible

The method permitted correct assessment of prognosis in only a proportion of cases even in the reports most favourable to RR There is no substantial evidence that RR is in any way related to the patient's general health or *immunologic response to the tumour or to the histologic type of malignancy* The production and progression of RR during radiotherapy suggest that it is an index of the sensitivity of the individual's squamous epithelium to irradiation and possibly also of the radiosensitivity of carcinoma arising from the squamous epithelium of the cervix

The important question therefore is whether or not the biologic response of a tumour to irradiation can be predicted from the radiosensitivity of non *malignant epithelial cells in vaginal smears from the same patient* An answer to this question demands general agreement not only on how the RR should be read but also on how the recordings should be evaluated It would appear to the writers that premenopausal cases should be considered separately from postmenopausal cases when RR is compared with incidence of recurrence cure rate etc Tumours at an advanced clinical stage should also not be considered together with early stage tumours Most important of all the RR values should derive from a defined period during irradiation or should be a mean of readings throughout the treatment period since RR is influenced by the progression of treatment Despite observation of these precautions, however no correlation between RR and survival in cancer of the uterine cervix was obtained in the present comparatively large series of cases.

## SUMMARY

Sensitization response (SR) and radiation response (RR) were studied in 720 patients treated for carcinoma of the uterine cerv SR was found to have no prognostic significance but was higher in postmenopausal than in premenopausal patients. The maximum and mean values of RR were also proved to bear no relation to the course of the disease The authors discuss the numerous factors influencing the radiation response (RR)

## ZUSAMMENFASSUNG

Die Empfindlichkeitsreaktion (SR) und die Bestrahlungsreaktion (RR) wurden bei 720 Patienten studiert, die fur Cervixcancer behandelt wurden. SR hatte keine prognostische Signifikanz, war aber deutlicher in Menopause als vorher. Auch die maximale und durchschnittliche Werte der Bestrahlungsreaktion zeigten keine Beziehung zum Krankheitsverlauf. Die Autoren besprechen die zahlreichen Faktoren die die Bestrahlungsreaktion (RR) beeinflussen.

## RÉSUMÉ

La réaction de sensibilisation (SR) et la réaction aux radiations (RR) ont été étudiées chez 720 malades traitées pour cancer d col de l'utérus. On constaté que la SR n pas de signification pronostique mais qu elle est plus forte chez les malades postménopausiques que chez les préménopausiques. On constaté aussi que les valeurs maximales et moyennes *de la RR sont sans relation avec l'évolution de cette affection.* Les auteurs examinent les nombreux facteurs qui influent la réaction aux radiations (RR)

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headings I to IV however it would seem that the apparent dependence of RR on the hormonal condition, on the clinical tumour stage, and especially on the progression of radiotherapy, may contribute to discrepancies in results if RR values are uncritically correlated to tumour curability

Clinical experience has shown that radiocurability in carcinoma of the cervix tends to be associated with various circumstances when treatment is begun — the patient s general health histologic type and clinical stage of the tumour immunologic host response and radiosensitivity of the neoplasm. If all these factors were known in the individual patient accurate prediction of the outcome would *presumably* be feasible

The method permitted correct assessment of prognosis in only a proportion of cases even in the reports most favourable to RR. There is no substantial evidence that RR is in any way related to the patient s general health or immunologic response to the tumour or to the histologic type of malignancy The production and progression of RR during radiotherapy suggest that it is an index of the sensitivity of the individual s squamous epithelium to irradiation and possibly also of the radiosensitivity of carcinoma arising from the squamous epithelium of the cervix

The important question therefore is whether or not the biologic response of a tumour to irradiation can be predicted from the radiosensitivity of non malignant epithelial cells in vaginal smears from the same patient An answer to this question demands general agreement not only on how the RR should be read but also on *how* the recordings should be evaluated *It would appear* to the writers that premenopausal cases should be considered separately from postmenopausal cases when RR is compared with incidence of recurrence cure rate etc. Tumours at an advanced clinical stage should also not be considered together with early stage tumours. Most important of all the RR values should derive from a defined period during irradiation or should be a mean of readings throughout the treatment period since RR is influenced by the progression of treatment Despite observation of these precautions, however no correlation between RR and survival in cancer of the uterine cervix was obtained in the present comparatively large series of cases.

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FROM THE DEPARTMENT OF PATHOLOGY AND ITS RADIOLOGIC LABORATORY
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# AUTOMATIC BODY-CONTOURING UNIT FOR DOSE PLANNING IN RADIOTHERAPY

by

KAI SETÄLÄ

The basic problems in radiotherapy remain the same, irrespective of whether irradiation is carried out by stationary (fixed-field) or rotation (moving-field, or moving beam) techniques, and, to a certain extent, irrespective of the quality of radiations, particularly in megavoltage therapy. Thus, when a malignant tumor within the body has been diagnosed, the extent of its spread and the degree of its radiosensitivity registered, and a final decision made either in favor of radical radiotherapy, combined treatment of some kind, or palliative radiotherapy, the following step in the execution of the plan of treatment is the determination of the topographic position of the tumor and of the adjacent non-affected tissues. However, before this can be done, one of the first procedures is the contour-casting, at one or more levels, of the body segment that contains the lesion, to obtain information on the exact anatomic form and shape of the enveloping part of the body through which irradiation is to be directed. This stage is of fundamental importance. Thus, in some instances, if the direction of the central ray is off by a few degrees, the tumor may be missed entirely or, at best, subjected to an inadequate dosage at one

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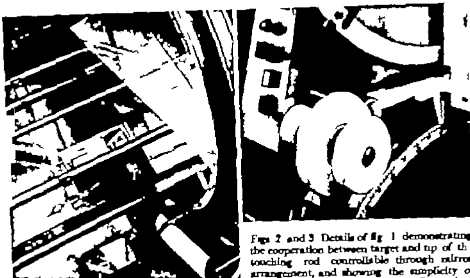
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Figs 2 and 3 Details of fig 1 demonstrating the cooperation between target and tip of th touching rod controllable through mirror arrangement, and showing the simplicity of the operation panel, from which all functions of the pparatus are directioned.

Of the techniques most commonly in use, the following principles may be mentioned

1 Series of standardized cut-out patterns (15) This technique is not however what would be desired, due in part to the fact that the patterns represent average bodies only and in part to their having been tailored according to cadavers. Death almost immediately in a significant manner alters the anatomical relationships of all soft tissues (the latin word arteria illustrates the situation well arteries were supposed by the ancients to contain air thus to be empty)

2. Plaster tapes or metal measures (10, 18 19)

3 Kerr dental moulding compounds (5 6)

4 Various types of devices consisting of a curved metal arm attached to a drawing board in such a manner that moving of the point of the arm manually along the particular contour of the body will draw the outline on the planning chart (14 31)

5. Lead-wire templates of various designs (16)

6. Individually prepared body casts in the form of coats or shells, made of plaster papier maché, plastic, or similar materials (7 22 "3 25)

7 Contour casts made on the basis of information obtained by transversal tomography (e. g 8 9 24) However the use of this technique has been criticized, because transversal tomography is possible only on standing and, partly on sitting patients, not on patients lying supine or prone.

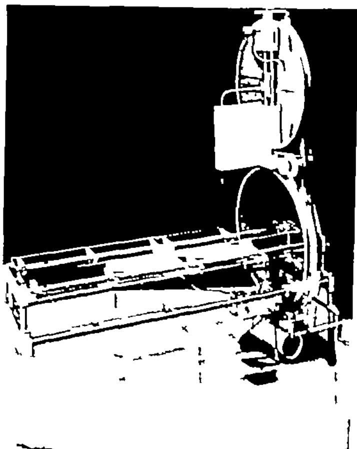
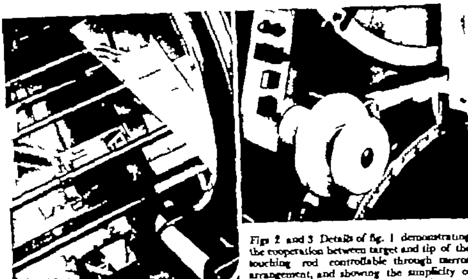


Fig 1 A general view of one of the prototypes for the automatic body-contour outlining unit for obtaining both transversal and sagittal cross-sections. The photograph represents a partial montage of three different aspects.

margin due to off-centering (reviewed e g in ref 25) It has been calculated (ref. 11) that the errors due to physical factors alone may accumulate approaching the 30 % range if they all happen to be in the same direction. A factor deserving serious attention lies in the fact that even average normal persons vary significantly in size shape composition and above all, in the symmetry asymmetry relationships of the body

The purpose of the present paper the first in this series is to describe a new equipment unit for an automatic rapid and reproducible delineation of life-size and true shape contour equivalents from any desired part of the body (26) The equipment may be used in megavoltage as well as in kilovoltage treatment.

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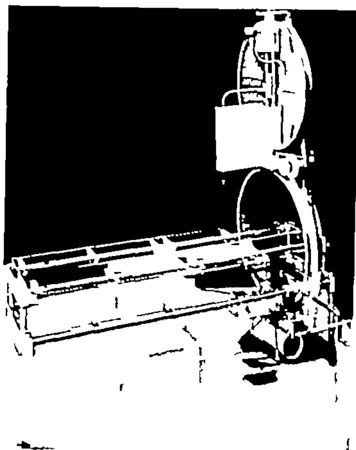


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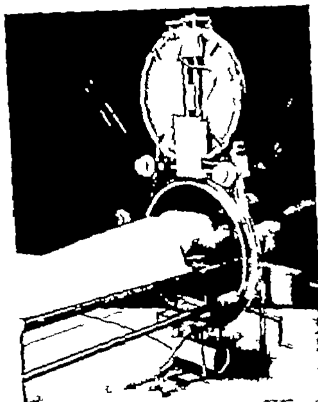


Fig. 5. A photographic montage, illustrating the obtaining of transversal body-contour equivalents. The patient lies perpendicular to the plane of the printing disc (cf. fig. 4).

printing disc, revolving simultaneously both around its own axis and making a circuitous satellite-like route concentrically with a guiding hoop-shaped structure. The rotator movements cooperate with a piece of equipment responsible for the movements of a rod that touches the skin surface. The latter makes a piston-like movement along a line passing simultaneously through the center of the printing disc on the one hand and through the center of the hoop-shaped girder on the other.

The distance of the examination table from the floor is adjustable in a perpendicular direction to allow for alterations on the horizontal reference plane. Since the back-pointer technique is not applicable to lying patients with lesions in the trunk, and since the pin-and-arc technique gives indirect information only, the examination table is constructed either of optically-free perspex glass (Fig. 1) or of wood equipped with an adjustable window. In

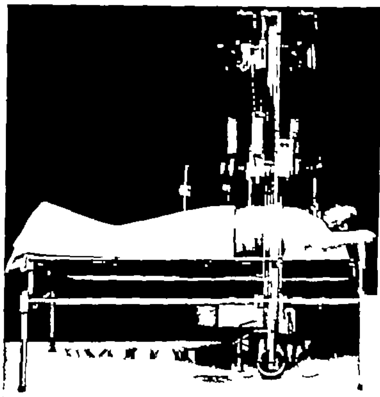


Fig 4 The pri ting pparatus including the touching rod is transferabl along the whol length of the examination table. The photograph represents montage of 3 portions of the movable part

8 Rectangular or arc formed metal or wooden frames that carry a large number of rods which pass through the stabilizing construction and touch the body surface (1—3 20 21 30)

Most of the techniques are applied in connection with separate equipment of various types, primarily intended for beam direction, such as back and/or front pointers and pin and arc devices.

## Present technique

A general view of one of the prototypes of the automatic body-contouring unit appears in Fig 1 Some technical details are shown in Figs 2 and 3 and the device in function is depicted in Fig 4 It is possible to obtain both transversal (Fig 5) and sagittal (Fig 8) body-contour equivalents The apparatus is composed of two principal elements one mobile and one immobile.

The mobile part, i e the apparatus for the automatic selfrecording of cross-sections is the most important (26) Its essential component is a rotating

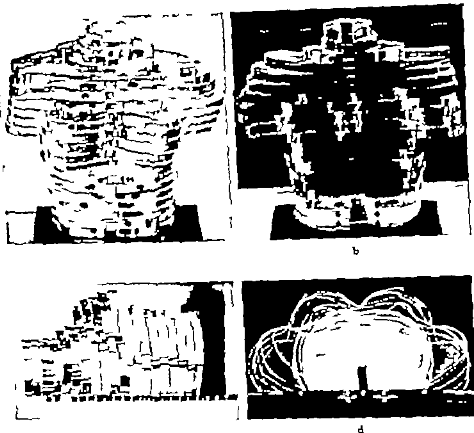



Fig. 7. Torso (chest) of translucent perspex glass designed according [illegible] he adult female subject in fig. 6 (the examination table as horizontal plane of reference, subject supine. ) and b) Ventral and dorsal aspects, ) lateral aspects, and d) the differing body-contour equivalents of he individual sections from the cephalad aspect. (Dosimeter insertion for experimental purposes can be carried out easily cf. ref. 28.)

symbols in the form of slides (illuminated hair cross, centigrade measure) sending an undistorted guiding light mark through the translucent examination table onto the desired landmark on the patient's skin the middle of the light mark is also centered upon the engraved median line on the table (2) a mirror arrangement permitting an exact selection of the relevant body segment and a continuous direct observation of the side and position of the patient, otherwise not visible to the operator (Fig. 2)

The rotating guiding hoop lies concentrically with the non-rotating structure. The angle of swing of the latter is a full circle (Fig. 5) The velocity of rotation

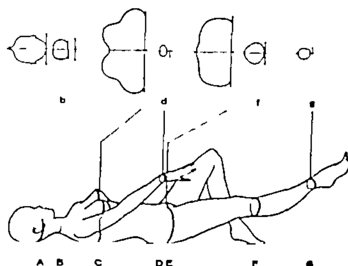



Fig 6 Transversal body-contour equivalents of an adult female through arbitrary levels, traced automatically on the planing chart examination table as horizontal plane of reference patient supine The drawing illustrates the usefulness of the apparatus in regard to both the trunk and the extremities.

the former case the translucent table is made up of several table leaves, set side by side which can be moved in the direction of the long axis of the table to obtain if needed a cleft between two adjacent leaves. Along the median line is engraved a full length longitudinal line as well as shorter cross lines at intervals of 10 mm that together serve partly as a system for the positioning of the patient — this is of the utmost significance particularly in patients with body deformities or suffering from spinal or hip disease (see ref 29) — partly as a body segment height indicator and partly as a coding system. When sagittal body-contour equivalents are to be printed the examination table seen in Fig 1 is either rotated 180 or it is kept stationary and a detachable auxiliary table (or tables) are placed along its long sides In both instances the patient lies parallel to the plane of the printing disc (Fig 8)

Beneath the examination table there are two longitudinal bars that carry the mobile part of the unit The carriage for the latter is the hoop-shaped construction 90 cm in diameter This element is non rotating but is equipped with ball bearings to allow its free transfer along the total length of the bars. The segmental level is adjusted by means of a hand wheel On the front of the hoop, a scale of angles 0 to 360 is engraved The degrees can be read from the indicator that synchronously follows the movement of the tip of the touching rod along the body surface contour

At the base of the carriage beneath the table two components are inserted (1) a light beam centering device (miniature projector) with exchangeable

The pearl-shaped tip of the skin-surface touching rod (Fig 2) is equipped with an extremely sensitive micro-switch. An electric impulse is generated when the tip comes into contact with the skin. The impulse activates the electronic motor-powered adjustment. This ultimately results in the printing of a mark on the printing (planning) chart thereafter the rod is instantaneously elevated. At a given point, which is adjustable, this movement stops and the tip redescends, hitting the skin again. Should the tip not hit the skin surface as often happens in the dorso-lateral and dorsal sectors of the neck and the sacral region of patients lying supine when transversal body-contour equivalents are prepared, the rod automatically stops at the perpendicular reference median plane and returns. When the tip is made to travel along the body contour the machinery records every individual piece of information onto the planning chart. The marks together form a body silhouette having the true size and shape. For obtaining sagittal body-contour equivalents, the touching rod *is equipped with, or replaced by* an *easily-insertable curved* arm having similar pearl-shaped tip and micro-switch as the original rod. This device functions according to exactly the same principles as that for obtaining transversal cross-sections. Fig 8 shows the manoeuver for obtaining sagittal body-contour equivalents. All movable construction elements are equipped with ball bearings and the mobile part of the unit has the proper counter balance weights for every position. If for some reason preferable, all operations can also be carried out manually

## Some applications of the unit

The situation is illustrated by examples. In obtaining the transversal body contour equivalents seen in Fig 6 the adult female subject was lying supine and the upper surface of the examination table served as the horizontal reference plane. This plane was adjusted so that the longitudinal line engraved on the table, and the line drawn (or tattooed) at the median line of the patient's back passed through the axis of the guiding hoop The cross-sections obtained were true-to-nature and reproducible time and again. The accuracy of the dimensions were verified with special caliper measures. Within the chest and abdominal parts, the respiratory movements were registered in the same planning chart. Printing of a transversal body-contour equivalent of 180° takes, on an average, 30 sec, that of 360 takes 45 to 60 sec, and that in the sagittal direction, about 45 sec. The thoracic part, designed according to the subject in Fig 6 is depicted in the supine position in Fig 7 In all, 21 individual transversal body-contour equivalents were printed at successive chest levels at 20 mm intervals in the cephalad-caudal direction.

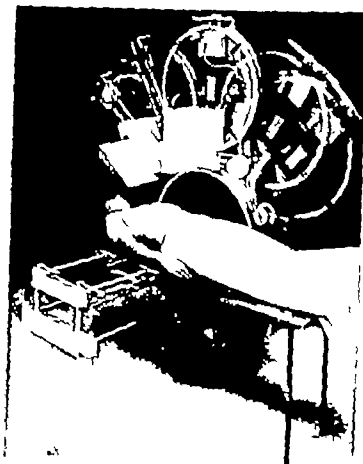


Fig 8 A photograph [illegible] ront ge, sh wing the manoeuver for obtaining of sagittal body-contou equivalents. The subject lies parallel t th pl n of the pri t ng disc (cf fig 5)

can be freely chosen At the back of the construction element an operating panel with selector switches, push buttons for regulating the work of the touching rod and pilot lamps indicating the various operating phases of the unit (Fig 3) are inserted Operation is possible from either side of the stand.

There is a rotating printing disc travelling around the rotating hoop with exactly the same radius as that of the rotating guiding hoop (Figs 1 5 and 8) When the guider is rotated the printing disc synchronously rotates at exactly the same velocity but in the opposite direction At the front of the disc a casette holder with a casette tray for printing paper and carbon papers and further apparatus for the movements of the touching rod and for the transfer of impulses to the final target (planning chart) are mounted The electronic part of the device contains among other parts relay sets and micro-switches responsible for the programmed functions

## SUMMARY

Presentation of new apparatus for dose planning in radiotherapy for the automatic, rapid and accurate obtaining of easily reproducible life-size, true-to-nature contour equivalents of any desired part of the body from lying patients. The function of the equipment is based on new principles. Examples of the pplication of the unit are given.

## ZUSAMMENFASSUNG

Beschreibung einer neuen Apparatus zu automatischer schneller und exakter Erziehung leicht reproduzierbarer lebensgrösser naturgetreuer Korperquerschnittsdiagramme für jeden beliebigen Körperteil zum Zweck der Dosisplanierung bei Strahlentherapie bei liegenden Patienten. Die Funktionsprinzipen des Gerätes sind neuartig Beispiele fur Benutzung sind angeführt.

## RÉSUMÉ

Pour déterminer les doses nécessaires en radiothérapie, l auteur conçu un pparell nouveau qui donne automatiquement, avec rapidité et précision, un tracé du contour du corps en grandeur naturelle. Le fonctionnement de cet pparell est basé sur des principes nouveaux. L auteur donne des exemples de son pplication.


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The whole procedure was carried out in the course of about 20 minutes. The sections were cut from translucent perspex sheets 20 mm in thickness and stacked on each other

The results of clinical series, including cancer in different regions of the body as well as certain other pathologic conditions, will be published later (ref. 27—29) However some general comments deserve mention here. Except for its original purpose — automatic recording of transversal and sagittal body contour equivalents — the unit can be employed for a number of other purposes, such as the registering and writing down of the exact localizations of entry and exit portals of the irradiation beam(s) Rapid and accurate control of the planned fields of treatment is possible both during the treatment period and after completion of the irradiation program. It is also of advantage to be able to follow up and record accurately from time to time, the progression or regression of pathologic conditions that cause alteration in some body contour e. g follow up of the response of goiter to treatment and that of alterations in thyroid cancer after radio-iodine therapy The present technique can also be used in the examination of pathologic changes localized in the abdominal and thoracic regions accumulation and resorption of serous cavity effusions, and changes in the size and form of the liver spleen and other organs. In addition it is possible to follow easily the alterations in the course of pregnancy by taking at given intervals, either a constant set of transversal outlines, or one or more sagittal body-contour equivalents, or both always at the same body regions Further the unit is applicable for anthropologic studies It is also possible to obtain silhouettes, e g from the patient's facial profile which are so circumstantial that the patient can be identified on the basis of these portraits

It is evident that outlining of transversal and sagittal body-contour equivalents is possible automatically and rapidly and without utilization of any correction factor whatsoever that might introduce sources of error By using carbon papers in the printing machine several copies are obtained simultaneously for immediate distribution to the relevant departments in the hospital Because the functions of the unit are programmed, the operations can be read directly from the respective indicators, the position of the patient and the relevant part of his body are easily re found and the data recorded in the hospital journal The printing device can further be installed to the new type treatment table now under completion in our laboratory Thereby the advantage is reached that we have at hand a unit which is simultaneously applicable both for obtaining body-contour equivalents and for radiation treatment and for different kinds of control purposes, without changing the position of the patient

FROM RADIUMHEMMET (DIRECTOR PROF. S. HULTBERG) STOCKHOLM, SWEDEN

# RADIOTHERAPY FOR CARCINOMA OF THE LUNG

by

ULLA BELING and JERZY EINHORN

The aim of this investigation has been to analyse the results of high-voltage radiotherapy in cases of inoperable carcinoma of the lung The material selected consisted of cases in which the lesion was undoubtedly a primary one and, if operation had been performed those in which fragments of tumour obviously remained. Radiotherapy was preceded by careful planning, and all the cases were followed up

*Material.* Between 1957 and October 1962, 457 patients had been referred to Radiumhemmet with a diagnosis of carcinoma of the lung 158 were selected for highvoltage radiotherapy and 20 of these were not included in the present material because there was no definite microscopic verification of the clinical diagnosis of malignancy because the microscopic examination revealed that it was not a primary lung tumour or because close scrutiny of the operation reports and histologic examination of the surgical specimens provided no conclusive evidence of any tumour tissue remaining after the operation

It had been found on the basis of the clinical and radiologic examinations, mediastinoscopy explorative thoracotomy and lymph-node biopsy that 124

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Table 1

*Survival times in different types of tumour*

| | Per cent survivals | | |
|---|---|---|---|
| | > 6 months | > 1 year | > 2 years |
| Squamous cell carcinoma | 49 | 30 | 8 |
| Oat cell carcinoma | 19 | 15 | 0 |
| Adenocarcinoma, alveolar cell carcinoma and unclassified | 39 | 18 | 2 |
| No metastases evident | 49 | 27 | 9 |
| Mediastinal metastases | 50 | 25 | 4 |
| Supraclavicular metastases | 30 | 6 | 0 |

T ble 2

*Survival times in the whole material and in a more homogeneous group after exclusion of cases of oat cell cancer or supraclavicular metastases*

| | Whole series | | Oat cell cancer and supraclavicular metastases excluded | | |
|---|---|---|---|---|---|
| | Per cent survivals | | Per cent survivals | | Per cent improved |
| Dose (R) | > 6 months | > 1 year | > 6 months | > 1 year | |
| 2 500—3 000 | 29 | 14 | 50 | 17 | 31 |
| 3 100—4 000 | 36 | 25 | 50 | 31 | 33 |
| 4 100—5 000 | 42 | 22 | 48 | 28 | 60 |
| 5 100—6 000 | 56 | 24 | 61 | 23 | 69 |
| 6 100—7 000 | 64 | 36 | 54 | 22 | 71 |

lymph node metastases, as in those without evidence of metastases, but shorter when supraclavicular metastases were present (Table 1)

Survival times and subjective improvement in groups receiving different radiation doses are shown in Table 2. A definite subjective and objective improvement occurred after radiotherapy in 60 % of the cases. The radiographic follow-up disclosed a definite regression of the tumour in 89 % of the cases.

In cases with signs of infection the results were poorer (Table 3)

Because of the tendency at this hospital to prefer surgical treatment, even in cases in which the possibility of radical operation is dubious, only cases with

of the cases were inoperable, 7 were recurrences at between 9 months and 7 years after operation and 7 had been referred because the operation had not been radical

Sixty three cases had squamous cell carcinoma 26 oat cell carcinoma 8 adeno-carcinoma, 2 alveolar cell carcinoma and 39 unclassified carcinoma of the lung

In 45 cases there were no clinical or radiologic signs of metastases at the beginning of the treatment, 76 had mediastinal metastases or involvement of the pleura or pericardium and 17 in addition had cytologically or histologically verified metastases in the supraclavicular glands Thirty-eight had high fever or other definite signs of infection

*Method* The irradiation had been given with a treatment unit loaded with a source of 2 000 or 4 000 curie $^{60}$Co The FSD was 70 or 80 cm. As a rule the treatment was preceded by careful planning the tumour dose was estimated from depth dose tables and the exit dose The daily tumour dose was 120 to 200 R the treatment being given on 6 days of the week for from 3 to 12 weeks, usually 6 to 8 weeks The radiation doses delivered are indicated in Table 2. The most common tumour dose was 5 100 to 6 000 R the highest being 7 000 R which was given in two cases over extremely long periods of treatment. In 13 cases conventional roentgen therapy (200 to 400 kV) had been given for less than one third of the tumour dose before high voltage therapy was started The total tumour dose in these cases was noted Twenty-five cases received treatment with cytostatics before or during the course of radiotherapy

The patients were checked regularly after the treatment. No case was lost to follow up Autopsies were performed in 50 cases.

## Results and Discussion

In 47 % of cases, the survival time was more than 6 months, in 22 % more than 1 year and in 5 % more than 2 years, Only 3 patients are still living two of them 2 years and one 3 years after the treatment all of them with metastases

Of the 50 cases who underwent autopsy 48 had metastases or tumour fragments at the original site and two who died at 9 months and 2 years after the treatment were considered to have succumbed to intercurrent disease in both instances acute pericarditis (cf MICHAILOV 1963)

The survival time was longest in squamous cell carcinoma and shortest in oat cell carcinoma It was approximately the same in cases with mediastinal

a more homogeneous material for analysis, the groups with shorter survival times were excluded, namely those with oat cell carcinoma or supraclavicular metastases (see Table 1) In the material remaining there was no difference in survival time between the groups receiving different irradiation doses. However also in this more homogeneous material the proportion of cases showing improvement increased with the dose (Table 2)

That the result was poorer in cases with signs of infection (Table 3) may admittedly have been due to the infection as such, but the infection and the shorter survival time could just as well have had a common cause, namely extension of the tumour

The results of radiotherapy for carcinoma of the lung was extremely poor in the present series, as it has also been in other large series (Table 4) The results of surgical therapy are also quite poor although prognostically favourable cases are selected for this form of treatment. Hence, in the great majority of cases judged by the surgeons to be inoperable, radiotherapy for carcinoma of the lung must be considered to be a palliative measure The results of radiotherapy might have been better with a material selected on a different basis (GUTTMAN 1964) but it must be borne in mind that lungs provide a very poor tumour bed for the following reasons there are no thick connective tissue septa, or layers of muscle by which the growth of tumour can be delayed continuous massage through breathing and abundant lymph drainage facilitate spread and metastasizing of the tumour metastases in the mediastinal tissue are difficult of access for both surgery and radiotherapy except for very poorly differentiated types, tumours of the lung are fairly resistant to this form of treatment, and the lung itself poorly tolerates irradiation

## SUMMARY

An analysis of the results of radiotherapy with $^{60}$Co in cases of inoperable, primary carcinoma of the lung is presented. The material selected for study comprised 138 cases doubtful cases were not included. In this material only 3 patients survived, all with metastases. There was no difference in survival time between cases treated with different doses in the range from 2 500 to 7 000 R. In 60 of cases, radiotherapy proved to constitute a good palliative measure.

## ZUSAMMENFASSUNG

Es werden die Ergebnisse der Therapie mit $^{60}$Co an inoperablen Karzinomen der Lunge untersucht. Das für diesen Studium ausgewählte Material umfasste 138 Fälle; zweifelhafte Fälle wurden ausgeschlossen. Von diesem Material überlebten nur 3 Patienten, alle mit Metastasen. Gleichgültig ob die Strahlendosis 2 500 R oder bis zu 7 000 R war gab es keinen Unterschied in der Überlebensdauer In 60 % der Fälle erwies sich die Strahlentherapie als eine gute palliativ Ersatzbehandlung

**Table 3**

*Survival times and improvement in cases with and without signs of infection*

| | Per cent survivals | | | Per cent improved |
|---|---|---|---|---|
| | 6 months | > 1 year | > [illegible] years | |
| Infection | 36 | 12 | 0 | 8 |
| No infection | 51 | 26 | 7 | 71 |

**Table 4**

*Comparison between series consisting of at least 100 cases in which radiotherapy for carcinoma of the lung had been given*

| Author and year | Type of irradiation | No. of cases | Per cent survivals | | |
|---|---|---|---|---|---|
| | | | 6 months | 1 year | > [illegible] years |
| Guttman 1953 | MeV | 100 | 63 | 27 | 4 |
| Haas et coll. 1957 | 250 kV | 143 | | 7 | |
| Schulz 1957 | 250 kV | 385 | 35 | 15 | 5 |
| Kutz 1958 | $^{60}Co$ | 173 | 57 | 24 | 7 |
| Krabbenhoft 1958 | 200 to 330 kV | 132 | | 1 | |
| Guttman 1958 | 2 MeV | 144 | 61 | 33 | 9 |
| Present series | $^{60}Co$ | 138 | 47 | 22 | 5 |

a poor prognosis remain for radiotherapy. On the other hand, the cases selected for high voltage radiotherapy constituted the best third prognostically of the 457 patients referred to Radiumhemmet.

If the surgeon's first assessment of the radicality of the operation had been accepted without checking, or if histologically doubtful cases had been included, the therapeutic results would have appeared better since some of the patients excluded on those grounds are still living with no signs of tumour. The decision as to whether the patient should be included in the series was reached on the basis of the surgeon's and pathologist's reports without knowledge of the prognosis in the individual cases.

It has been claimed that higher irradiation doses give better results in carcinoma of the lung (Kutz 1958, Guttman 1958, 1961, 1964). This appeared to be true on the first scrutiny of the present material. The mean survival time increased with the radiation dose (Table 2). This, however, may be due to the fact that prognostically less favourable cases received a smaller dose. To obtain

a more homogeneous material for analysis, the groups with shorter survival times were excluded namely those with oat cell carcinoma or supraclavicular metastases (see Table 1) In the material remaining there was no difference in survival time between the groups receiving different irradiation doses. However also in this more homogeneous material the proportion of cases showing improvement increased with the dose (Table 2)

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## RÉSUMÉ

Les auteurs analysent les résultats de la radiothérapie par le $^{60}$Co dans des cas de cancer primitif inopérable du poumon. Ils ont retenu 138 cas pour cette étude et ont éliminé les cas douteux. Sur ce matériel, trois malades seulement ont survécu, tous atteints de métastases. La durée de survie a été la même pour les cas traités par des doses différentes comprises entre 2 500 et 7 000 R. Dans 60 % des cas la radiothérapie s'est montrée un bon moyen palliatif.

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# TWO SPECIAL APPLICATIONS OF HIGH ENERGY ELECTRON BEAMS

by

SVEN HULTBERG, RUNE WALSTAM and PER ERIK ÅSARD

Electron beams from betatrons and linear accelerators have for some time been used at many centres for therapy and their essential physical properties are fairly well known. Although opinions may widely differ as to the relative merits of this irradiation method, there seems to be general agreement on some of its advantages and limitations. It is possible by the introduction of special techniques, to widen the range of cases in which the electron beam can be utilized.

Clinical experiences from the use of electron beam therapy were discussed by HULTBERG (1962) at the International Congress of Radiology in Montreal. The paper presented at this meeting was based on work with a Siemens 15 MeV betatron which had been installed at Radiumhemmet in November 1957. Two special techniques were mentioned; they had been worked out in the department for clinical radiation physics in the years 1958 and 1959. These techniques will now be described in more detail.

One is a simple method introduced for improving the uniformity of the dose

This work was presented in part at the Xth Internat. Congress of Radiology in Montreal 1962 and at the 25th Meeting of the Nordic Society of Medical Radiology, Odense, Denmark, in 1963. Submitted for publication 18 September 1964.

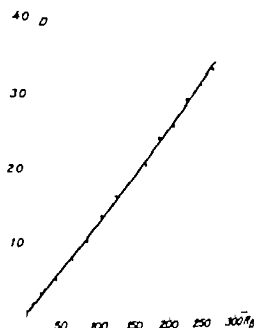



Fig 1 Density of N51 film as a function of exposure at the depth dose maximum in a phantom irradiated with 15 MeV electrons

distribution when areas have to be irradiated which are larger than those that can be covered with an ordinary single treatment tube The other technique aims at rendering possible the use of the special properties of the electron beam for the irradiation of intraorbital tumours.

*Measuring technique* In the dose distribution studies a film with a thin emulsion Gevaert Dipos N51 was employed This film was calibrated with a 100 R Victoreen chamber and showed good linearity between film density (at least up to a density of 3 0) and exposure measured with the ionization chamber at the depth dose maximum in a phantom (see Fig 1) using a provisional $R_\beta$ unit. This unit was obtained by employing the $^{60}$Co-R factor for the Victoreen chamber in the case of electrons as well Work is in progress for converting this "home made $R_\beta$-unit into rad.

Perspex was used as the main phantom material and the films were exposed in planes both parallel and perpendicular to the central beam axis. The films were covered with black perspex in order to prevent blackening of the film due to Cerenkov radiation.

Since films exposed in a plane parallel to the beam axis will show too low density in the build up region (MARKUS 1959) this density was corrected by a factor obtained from defining

density with perpendicular film

density with parallel film

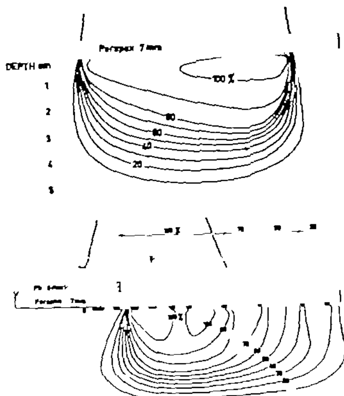



Fig. 2. Comparison of dose distributions as obtained with single standard beam of 12 MeV electrons with 12 × 8 cm field (upper diagram) and by application of the 'overlapping field' technique using the same beam size (lower diagram)

as given by LOEVINGER et coll. (1961) This factor when calculated on the basis of results from our measurements with the N51 film, was for instance found to be 1 10 at a depth of 2 mm in the phantom, on irradiation with 12 MeV electrons using a tube of 3 cm diameter

## Electron beam irradiation of large fields

If the area to be irradiated is larger than that of the standard collimating tubes, the whole area can be covered by dividing it into several fields to be irradiated separately There is a certain risk involved with this method if considerable inhomogeneity in dose distribution arises at the boundaries between the fields. In order to reduce such inhomogeneity a technique has been developed in analogy with the overlapping technique described by WALSTAM

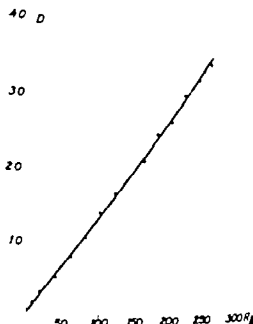



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$$\frac{\text{density with perpendicular film}}{\text{density with parallel film}}$$




Fig 4 NS1 films from irradiation of phantom with 12 MeV electrons using tube of 3 cm diameter During exposure of the film show in (b) lead absorber 6 mm thick and 8 mm in diameter was placed i the phantom with its axis parallel with the obliquely incident beam.

error of $\pm$ 1 cm. It is obvious that due to the scattering of the electrons the dose inhomogeneities will be less with increasing depth than the theoretical maximal error

An example of this technique, applied clinically for the treatment of recurrence in the skin of a breast cancer is illustrated in Fig 3 The treatment area, which was 12 × 18 cm, was irradiated daily through three adjacent 12 × 8 cm fields, the two border lines between the fields being displaced 1 cm each day thus on the sixth treatment day the patient was irradiated on fields 6 14 and 22 as illustrated in the figure The lateral boundaries of the treatment area were covered with a lead absorber when the patient was irradiated on fields 1 to 7 and fields 19 to 25 in order to get sharp lateral boundaries, as illustrated to the left in Fig 2. The total treatment therefore consisted of 25 irradiations (in 8 sessions) with a 1 cm step-wise movement this theoretically produced a maximal dose inhomogeneity due to overlapping of $\pm$ 13

Clinical observations of the effect of dose inhomogeneities at the border between two stationary standard fields that were intended to cover a larger area indicate that there is a real risk of the tumour being unaffected by the radiation at the boundary region between two fields. This has for instances been observed in the treatment of the parasternal region with two standard fields separated by 0.5 cm and there is good reason to believe that the cause was a too low dose having been received by the area concerned. When the technique now described is used, there is considerably less risk of underdosage or overdosage.

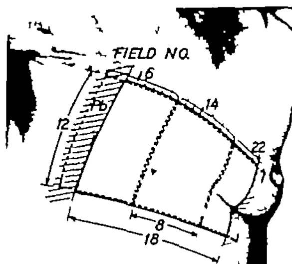



Fig 3 Th overlapping field techniqu cli ically applied to a patient with metastases from a ma mary carcinoma The broken lines ndicat the positions of f elds 6 14 and 22 on the 6th irradiation day The total area treated was 12 × 18 cm.

(1958) for use with the decacurie apparatus. The underlying principle of this method is to simulate a moving beam by applying several stationary fields. In this manner it is possible to achieve a fairly uniform dose distribution even in the irradiation of irregular surfaces. Moving beam techniques are in the main most suitable for irradiation of plane surfaces when the whole area can be covered by the beam (TRUMP et coll 1953) or when the surface fits the radius of an arc therapy set up (BECKER et coll 1956)

The overlapping field technique is exemplified in Fig 2 from which a comparison may be made between the dose distribution in a standard field of 8 cm width and that obtained with six overlapping standard fields of the same size as a result of moving the tube a distance of 2 cm between each exposure As may be seen from this figure a sharp boundary has been produced on the left hand side by covering the adjacent area with lead to protect it from portions of the field being outside of the area to be irradiated If lead protection is not employed, a diffuse border such as that shown on the right hand side of the figure will be obtained The measurements illustrated in Fig 2 were made in a mix D phantom and the perspex plate at the beam aperture was used in order to avoid the small but significant build up region which is considered unsuitable in some kinds of treatment

When two adjacent standard fields are irradiated the maximum dose inhomogeneity that can occur is ± 100 % By using the overlapping technique the maximum inhomogeneity will be $\pm S/L \times 100$ % where $S$ is the distance the field is moved between each exposure and $L$ is the length of the field in the same direction Thus, in this example the maximum error will be $2/8 \times 100 =$ $= 25$ % on the assumption that the fields can be moved with a maximum



b

Fig 4 N31 films from irradiation of phantom with 12 MeV electrons using tube of 3 cm diameter During exposure of the film shown in (b) lead absorber 6 mm thick and 8 mm in diameter, was placed in the phantom with its axis parallel with the obliquely incident beam.

error of $\pm$ 1 cm. It is obvious that due to the scattering of the electrons the dose inhomogeneities will be less with increasing depth than the theoretical maximal error

An example of this technique, applied clinically for the treatment of recurrence in the skin of a breast cancer is illustrated in Fig 5 The treatment area, which was 12 × 18 cm, was irradiated daily through three adjacent 12 × 8 cm fields, the two border lines between the fields being displaced 1 cm each day thus on the sixth treatment day the patient was irradiated on fields 6 14 and 22, as illustrated in the figure. The lateral boundaries of the treatment area were covered with a lead absorber when the patient was irradiated on fields 1 to 7 and fields 19 to 25 in order to get sharp lateral boundaries, as illustrated to the left in Fig 2 The total treatment therefore consisted of 25 irradiations (in 8 sessions) with a 1 cm step-wise movement this theoretically produced a maximal dose inhomogeneity due to overlapping of $\pm$ 13 %

Clinical observations of the effect of dose inhomogeneities at the border between two stationary standard fields that were intended to cover a larger area indicate that there is a real risk of the tumour being unaffected by the radiation at the boundary region between two fields. This has for instances been observed in the treatment of the parasternal region with two standard fields separated by 0.5 cm and there is good reason to believe that the cause was a too low dose having been received by the area concerned. When the technique now described is used, there is considerably less risk of underdosage or overdosage.

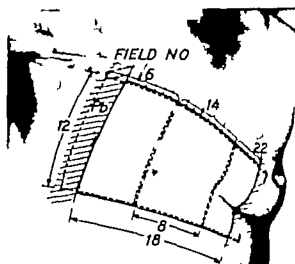



Fig 3 The overlapping field technique clinically applied to a patient with metastases from mammary carcinoma. The broken lines indicate the positions of fields 6, 14 and 22 on the 6th irradiation day The total area treated was 12 × 18 cm.

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Fig. 6. Lead absorbers applied in different positions on contact eye glasses.



Fig. 7 The contact glass, with attached lead absorber and securing threads, applied to the eye of a patient.

An example of the dose distribution in a cross-section of an eye, obtained by two electron beams with oblique incidence, is given in Fig 5. The dose in the protected area derives both from the scattered electrons and the bremsstrahlung from the lead applicator as well as from the betatron itself. The bremsstrahlung contribution from one field, with the energies concerned, 6 to 12 MeV and the beam size used can be estimated to be less than 5 % of the dose maximum (HAGEMANN & LÖHR 1961)

On clinical application of the method described, lead absorbers are glued on to contact glasses, of the kind used in electroretinologic investigations, as shown in Fig 6. The contact glass, with its lead absorber is applied to the patient's eye under local anaesthesia and may be attached by means of three threads (Fig 7) Treatment can be planned individually for each patient,

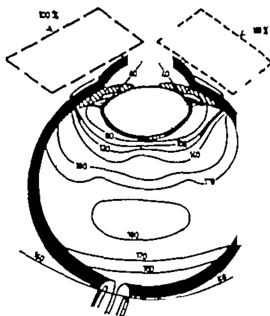


Fig 5 Dose distribution obtained when using two coplanar electron beams with lead shields combined on a sectional schematical drawing of an eye. The position of the lead absorbers as well as the beam directions are indicated.

The overlapping field technique has proved very useful in irradiation of widespread metastatic nodules in the chest wall of intermammary lymph nodes and in postoperative irradiation following radical mastectomy. We have so far not observed any lung fibrosis occurring after electron beam irradiation of this type when using a dosage of 4 000 $R_\beta$ (maximum) over two weeks.

## Irradiation of intraorbital tumours

With the technique adapted for irradiation of intraorbital tumours we aim at making use of the scattering and absorption properties of high energy electrons which are especially suited for irradiation of tumours of the eye since then one of the main problems is to protect the lens from radiation induced cataract.

Two films, irradiated with 12 MeV electrons using a tube of 3 cm diameter are shown in Fig 4. The one in (a) represents an ordinary exposure with the beam axis perpendicular to the phantom; it shows the typical electron absorption pattern. The film in (b) was exposed with a 6 mm high cylindrical lead absorber placed on the phantom with its axis parallel with the obliquely incident beam. As may be seen from the blackening of this film the electrons are scattered under the eccentrically placed lead absorber although the volume immediately beneath the applicator representing the position of the lens, was protected. The actual irradiation technique aims at combining two or more such beams in such a way that the percentage dose in the tumour mass will become as large as possible compared to the dose received by the lens.

## SUMMARY

A method for irradiation of areas larger than those covered by the largest standard treatment tube on the Siemens 18 MeV betatron, and special technique for irradiation of intraorbital tumours, are described. Examples of clinical applications are given.

## ZUSAMMENFASSUNG

Eine Bestrahlungsmethode, die für grössere Felder geeignet ist als die die mit den grossten Standard-Tubume von Siemens 18 MeV Betatron bestrahlt werden können, als auch eine Spezialtechnik zur Bestrahlung von intra-orbitalen Tumoren, werden beschrieben. Beispiele für die klinische Anwendbarkeit werden gegeben.

## RÉSUMÉ

Description d'une méthode d'irradiation de surfaces plus grandes que le plus grand des tubes standard de traitement du bétatron de 18 MeV Siemens, par une technique de chevauchement des champs, et présentation d'une technique d'irradiation des tumeurs intra-orbitaires, préservant le cristallin.


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suited to the size and position of the tumour by having access to contact glasses with differently placed lead absorber and by choosing suitable angles of incidence and electron beam energies. Adult patients may facilitate the irradiation procedure by holding the eye fixed in a suitable direction during the treatment Children are treated under anaesthesia although the procedure is then complicated by the necessity of getting the eye into the desired position. So far however it has always proved possible to carry out the irradiation without undue difficulty

## Case reports

*Case 1* A girl, aged 3 years, with a retinoblastoma affecting nearly half of one eye was treated in February—March 1959 a tumour dose of 4 × 400 $R_\beta$ from a 1? MeV electron beam applied over 6 days and using the lead shield. Conventional roentgen radiation was added through a lateral portal with a tumour dose of 2 000 R over 2 weeks. Three months later (in June) only slight regression was evident an additional series of 3 × 400 $R_\beta$ electrons and 1 000 R roentgen radiation was then applied At the end of August 1959 only small remnants of the tumour mass could be observed. In April 1960, an ophthalmologist in another country enucleated the eye for probable malignancy Some opacities were present, and there was slight hemorrhage but no tumour could be found and the lens was undamaged.

*Case 2* A boy aged 12 months was treated for retinoblastoma in October 1959 according to the same principles as the girl but with the tumour dose increased to 2 800 $R_\beta$ electrons over 3 weeks combined with 1 500 R conventional roentgen radiation Three years later only a very small remnant of the tumour was seen, with a protrusion of 2 dioptries as compared to 9 dioptries when irradiation was started. Four and a half years after the treatment there was no longer any protrusion of the tumour region, and only a few small calcifications could be seen. A small posterior cataract was present but did not give the boy any trouble.

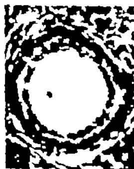
*Case 3* A boy aged 6 months, with gliomatous masses affecting more than half of one eye and with surrounding secondaries, did not respond well to the irradiation which was tried only because the parents refused enucleation The child died about 7 months after the treatment

*Case 4* A boy aged 8 months, with a retinoblastoma affecting the temporal half of one eye was treated with 12 MeV electrons three times a week for a month towards the end of 1962 The total tumour dose was 3 600 $R_\beta$. The tumour has gradually regressed the patient is still under observation and as long as the improvement continues no more irradiation will be administered. No cataract has been observed

Though the number of patients treated so far are too few to allow a definite assessment of the value of the method the technique appears promising and seems to be worthwhile trying out further

Independently of this investigation BECKER & BAUM (1960) have worked out a technique that is similar in some particulars but differs in certain details. So for instance is an iron absorber applied inside the treatment tube for protection of the eye during electron irradiation of tumours in the dorsal region of the eye











Oocyte with 3 follicular cells (Fig. 1) and oocyte with 5 follicular cells (Fig. 2) both H-E. × 1 000.
Primary follicle oocyte surrounded by one complete layer of follicular cells (Fig. 3) (H-E. × 500)
Growing follicle with two layers of follicular cells (Fig. 4) (H-E. × 400)
Growing follicle with two layers of follicular cells and early antrum formation (Fig. 5) (H-E. × 250).
Growing follicle with three complete layers of follicular cells (Fig. 6) (H-E. × 400).
Graafian follicle (Fig. 7) (H-E. × 250).

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# EFFECT OF RADIOSTRONTIUM ON OOCYTES AND FOLLICLES OF ADULT MICE

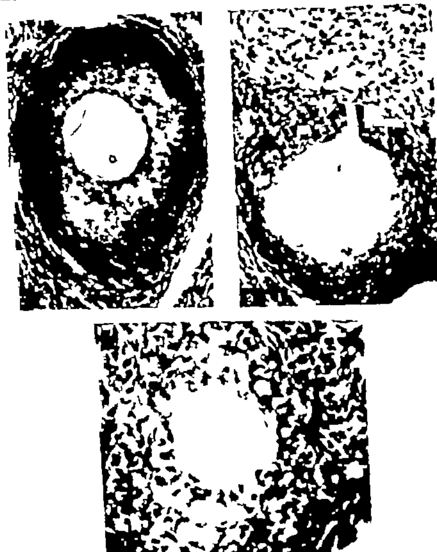
by

B. HENRICSON and A. NILSSON

Already in 1907 BERGONIÉ & TRIBONDEAU reported that oocytes in early stages of development were sensitive to external radiation, observations confirmed histologically in mice by e. g. BRAMBELL et coll. (1927), OAKBERG (1958, 1960, 1962), PETERS (1961), PARSONS (1962), PETERS & LEVY (1964). RUSSELL et coll. (1959) found that the effect on fertility was much greater if the mice were irradiated when immature rather than as adults.

Young oocytes without a complete layer of follicular cells are more sensitive, whereas later stages of follicular development seem to be more resistant. Different sensitivity also exists among the developmental stages of young oocytes (OAKBERG 1960, 1962, PETERS 1961, PETERS & LEVY 1964). Acute irradiation is more effective than chronic irradiation in both young and adult females. As oocytes in young mice pass through extremely sensitive stages of short

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Degenerating follicle. Pycnotic and lytic cells in follicular layers. Shrunken oocyte with disintegration of zona pellucida (H-E. × 250) (Fig. 8)
Late stage of follicular degeneration (H-E. × 250) (Fig. 9).
Corpus atreticum (H-E. × 400). (Fig. 10)

*Corpora atretica* were also counted. These (Fig. 10) represent the visible end result of atresia in growing and Graafian follicles. The changes consist mainly of a highly degenerated oocyte surrounded by a glass membrane and peripheral to this some theca cells and connective tissue.

duration chronic irradiation can however be highly effective since all young oocytes are exposed during these stages.

A significant improvement in fertility of female mice has been observed with dose fractionation (RUSSEL et coll 1957) A further increase in reproductive performance is obtained if the radiation is given continuously at low intensity (RUSSELL et coll 1959)

Information about the effect on the ovary of internal emitters is not very detailed BLOOM (1948) in a series of mice, rats and rabbits injected intra peritoneally with dosages between 0 5 and 3 6 $\mu$Ci/g bodyweight of $^{90}$Sr reported no significant effect on the ovary On the other hand this author stated that radium (0 3 $\mu$Ci/g) and plutonium (0 03 $\mu$Ci/g) cause extreme damage to the ovary $^{32}$P and $^{131}$I are also effective in causing damage to ovarian follicles (MURPHREE et coll 1952 and HUGH 1954 respectively)

The object of the present work was to gain more detailed information about the action of internal radiation on the mammalian ovary

*Material and Methods* Inbred female CBA mice were injected intravenously at the age of 75 days with 0 7 $\mu$Ci Sr per gram bodyweight The dosage corresponds to that used in our studies in male mice (HENRICSON et coll 1962, HENRICSON & NILSSON 1964)

Five mice were sacrificed at 6 intervals of 7 days each with a last group of 5 at 56 days after treatment. Control groups of 5 mice each were killed at the age of 75 + 7 75 + 21 75 + 35 and 75 + 56 days. The ovaries were fixed in Stieves fluid immediately after killing The right ovary was serially sectioned in 10 $\mu$ sections with 100 $\mu$ between consecutive sections.

The following types of oocytes and follicles were identified and counted.

| | |
|---|---|
| Oocytes group I | Oocyte with 0—4 follicular cells (Fig 1) |
| Oocytes group II | Oocyte with 5 follicular cells to almost complete single layer follicular epithelium (Fig 2) |
| Primary follicles | Oocyte surrounded by one complete layer of follicular cells (Fig 3) |
| Growing follicles | Two (Fig 4) or more (Fig 6) layers of follicular cells without complete formation of an antrum |
| Graafian follicles | Complete antrum formation in the folllcular epithelium (Fig 7) |

All these types of oocytes or follicles were classified as normal and degenerated or atretic. Common histologic signs of karyolysis or karyopyknosis were taken as criteria of degeneration in oocytes or follicular cells (Figs 8 and 9) Degeneration of the oocytes has also appeared in the form of vacuolized and coarse granulated or shrunken cytoplasm with changed affinity to stain

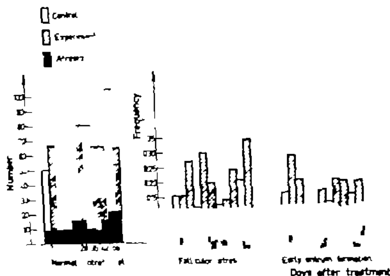



Fig 12. Average number of growing follicles, frequency of atresia and early antrum formation (cf. text) per ovary of five mice different ages.

with Graafian follicles (Fig 13a) This holds for the total number as well as for the frequency of atresia. A tendency to more numerous Graafian (and also growing) follicles in mice at 7 and 21 days after treatment might be meaningful and will be dealt with in the discussion.

Finally the numbers of corpora atretica have been considered in treated mice versus controls (Fig 13b) These are definitely more numerous in the experimental group

## Discussion

Ovaries subjected to $^{90}$Sr $\beta$-rays contain definitely fewer oocytes without a fully developed follicular epithelium. This could be considered a criterion of oocyte death as a consequence of an acute action of the strontium introduced. A similarity following roentgen treatment should then exist. Very few direct signs of degeneration have been noted but this could be explained by the fact that there is an interval of at least 7 days between treatment and evaluation. According to PARSONS (1962) necrotic debris is removed within 24 hours. The acute accumulation of $^{90}$Sr in testicular tissue is almost completely faded away during the first 24 hours (HENRICSON et coll. 1962) and a similar outcome in the ovaries could very well be assumed.

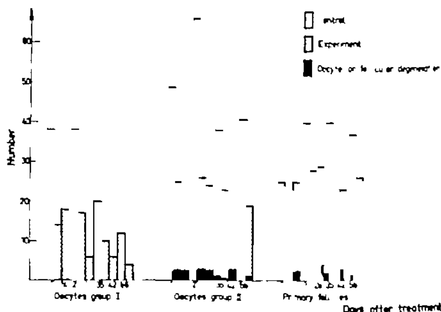



Fig 11 Average number of oocytes group I and II (cf text) and primary follicles per ovary of five mice at different ages.

We have also indicated follicles with what we call early antrum formation in growing follicles with two layers of follicular cells The intercellular tissue (Fig 5) in the stratum granulosum is loose and may represent the initiation of formation of large pools of follicular liquid characteristic of Graafian follicles with three or more layers of granulose cells

## Results

The average numbers of oocytes and primary follicles in 5 mice at different periods after treatment are given in Fig 11 Degeneration of oocytes or follicular cells was very rare in the control material and also represented a minor fraction in treated animals The reduced number of oocytes in these latter is obvious The decreasing oocyte number of groups I and II by age is apparent in the controls and to almost the same extent in the ovaries subjected to strontium treatment A corresponding increase of primary and growing (Fig 12) follicles with age can be traced at least in normal animals

In Fig 12 the total numbers of normal and atretic growing follicles and the frequency of the last mentioned type are given The frequency of early antrum formation has also been indicated Atresia as well as early antrum formation are more frequent in treated animals

No uniform difference is evident between the treated animals and controls

number of corpora lutea and implantation sites as well as a somewhat higher fetal mortality. The present results should also be comparable to those reported by RUGH et coll. (1959) as a consequence of continuous low intensity external radiation. On the other hand, the treated ovaries will be depleted of follicles much more quickly.

## SUMMARY

Female CBA mice have been injected intravenously with 0.7 μCi $^{90}$Sr per gram bodyweight at the age of 75 days. The predominating effect seems to have been an increased rate of development of oocytes into follicles and of these into later follicular stages. A certain lethal effect on young oocytes cannot be excluded.

## ZUSAMMENFASSUNG

Weibliche CBA Mäuse erhielten ein intravenöse Injektion von 0.7 μCi $^{90}$Sr per Gramm Körpergewicht im Alter von 75 Tagen. Der vorherrschende Effekt war anscheinend eine zunehmende Umwandlung der Oocyten in Follikel und wiederum von diesen in die späteren Stadien der follikulären Entwicklung. Ein teilweiser lethaler Effect uf ju ge Oocyten kann nicht völlig ausgeschlossen werden.

## RÉSUMÉ

Des souris femelles CBA ont reçu à l'âge de 75 jours une injection intraveineuse de 0.7 μCi de $^{90}$Sr par gramme de poids corporel. L'effet prédominant semble avoir été une accélération de la transformation des oocytes en follicules et de ces derniers en stades folliculaires plus avancés. On ne peut pas exclure un certain effect léthal sur les jeunes oocytes.

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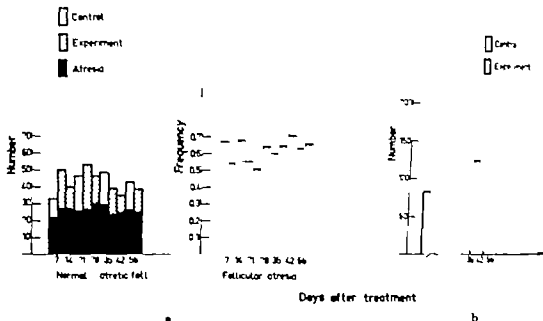


Fig 13. Average number of Graafian follicles and frequency of atresia ( ) and verage number of corpora tretica (b) per ovary of five mice at different ages.

It is necessary however to consider another possible explanation of the reduced number of oocytes — it might be caused by an increase in their rate of development into follicles There are at least two good criteria for an increased follicular development of growing and Graafian follicles. The first evidence is that of antrum formation in growing follicles, more frequent in the treated group (Fig 12) There is also an obvious predominance in the number of corpora atretica in the treated groups (Fig 13b) in fact this predominance is large enough to compensate for the loss of oocytes and follicles which can be seen if all types of oocytes, follicles and corpora atretica are collected. The total number of Graafian follicles and the frequency of atresia in these are about the same in the treated group and the controls (Fig 13a) This could hardly be the case if the younger oocytes had been more or less eliminated. A third sign of a more rapid follicular development might be that at days 7 and 21 the growing (Fig 12) and Graafian (Fig 13a) follicles tend to be more numerous in the treated group

With this discussion in mind it would not be surprising to find an increased ovulation rate and possibly also an increased rate of implants in mice treated with the dosage of • Sr used This conclusion seems to agree with preliminary results obtained by LÜNING & FRÖLÉN (1964) in a series of female mice mated after •Sr treatment These authors reported a tendency towards an increased

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# RADIOMERCURY AND RAT KIDNEY

## An autoradiographic study with Neohydrin $^{203}$Hg

by

L. LAAKSO, I. LINDGREN and A. REKONEN

GREIF et coll. (1956) and BORGHGRAEF et coll. (1956) have reported that radiomercury administered as Neohydrin-$^{203}$Hg was localized and retained in the kidneys of rats and dogs. This phenomenon of long retention was used for the demonstration of the human renal parenchyma by detecting the radioisotope by means of a scintillation scanning technique (MCAFEE & WAGNER 1960). Interest in this method has recently revived as it is felt that it may help in the localization of disease processes and in obtaining biopsies from the kidneys (TELFER et coll. 1964, POREN et coll. 1964).

Two of us (L. L. & A. R.) have carried out some clinical pilot studies with this method but it seemed pertinent first to study microscopically the localization of the radiomercury in renal tissue so as to determine which parts of the kidney are made visible by the method. Furthermore, in calculating the radiation dose to the kidney it is important to know whether the whole or only a part of the organ accumulates the radioisotope.

Part of this work was aided by a grant to one of the authors (I. L.) from the Sigrid Jusélius Foundation. Submitted for publication 19 November 1964.

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Fig. 3. Autoradiogram of kidney 6 hours after the injection of 2 μCi Neohydrin-$^{203}$Hg. The activity is located only to the cortex, mostly in the corticomedullary zone.

The microscopy study of the autoradiograms from the kidneys showed that the injected radioisotope was localized in the renal cortex, mainly in its medullary part (Fig. 3). It was evident from high resolution autoradiography that the silver granules were lying above the tubules and that the distal convoluted tubules had accumulated most of the substance. The medulla and the glomeruli displayed no activity (Fig. 4). The autoradiograms from the liver had a diffuse pattern of radioactivity distribution.

## Discussion

The results indicate that the radioisotope Neohydrin-$^{203}$Hg accumulates exclusively in the renal cortex and that therefore it is only the cortex that is shown when this substance is used for the demonstration of the renal parenchyma in a scanning technique. All pathologic processes demonstrable by this method lie in the renal cortex, and tissue changes in the medulla are revealed only indirectly and if they deform the cortical structure.

Consideration must be given to the fact in calculating the radiation dose in renal tissue after the administration of Neohydrin-$^{203}$Hg that no radioiso-

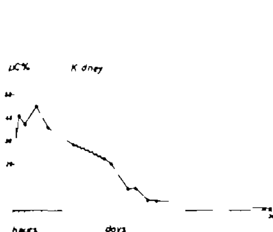



Fig. 1. Accumulation of radioactivity in the kidney after intraperitoneal injection of Neohydrin $^{203}$Hg. Values are given as percentages of the dose injected.

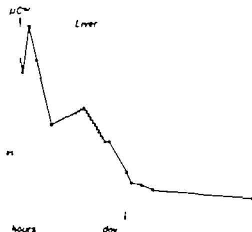



Fig. 2. Accumulation of radioactivity in the liver after intraperitoneal injection of Neohydrin $^{203}$Hg. Values are given as percentages of the dose injected.

*Material and Methods.* Eighteen Wistar rats of 250 g mean bodyweight received by single intraperitoneal injection 2 μCi of Neohydrin $^{203}$Hg (specific activity 75 mCi/mg Neohydrin) dissolved in 0.5 ml physiologic saline. The rats were killed after intervals of 1/2, 1, 2 and 6 hours and 1, 2, 5, 10 and 30 days. The kidneys and the liver were dissected out, fixed in formalin 10 % and processed through alcohol and xylene to paraffin blocks. Sections, 5 to 7μ thick, were mounted on clean glass slides, the autoradiographic stripping film technique being used. Two types of photographic material were employed: Kodak AR 50 for low resolution autoradiography and Kodak AR 10 for high resolution autoradiography. The exposures were made at a temperature of 4° C and the time varied between 1 and 3 months. The films were developed in Kodak D-170 solution (20° C, 3 min) and fixed in the ordinary way. Finally, the autoradiograms were stained with haematoxylin and celestin blue.

The radioactivity was measured from whole organs in a well type counter with 2 μCi doses as controls. The maximum limit of error for this method is ± 10 %.

## Results

The accumulation of radioactivity in the kidney and liver after a single injection of 2 μCi Neohydrin $^{203}$Hg is illustrated in Figs. 1 and 2. The quantitative values show that the kidney accumulates much more of the substance than the liver. The fall-off in the kidneys begins at 6 hours.

## ZUSAMMENFASSUNG

Die Verteilung des radioaktiven Neohydrin-$^{203}$Hg wurde an der Rattenniere mittels Autoradiographie und Scintillometrie studiert. Die Radioaktivität nahm im Nierengewebe rasch zu und war lediglich in der Cortex konzentriert, vorwiegend in den distalen Tubuli renales. Die Strahlungsintensität der Cortex wird daher wenigstens um 30 % stärker als diejenige die unter der Annahme berechnet ist, dass die Aktivität gleichmässig über die ganze Niere verteilt sei.

## RÉSUMÉ

La distribution de la néohydrine radioactive $^{203}$Hg a été étudiée sur le rein du rat par autoradiographie et par des mesures scintillométriques. La radioactivité s'accumule rapidement dans le tissu rénal et se localise uniquement dans la corticale, surtout dans la partie distale des tubes contournés. C'est pourquoi la dose de radiation reçue par la corticale est au moins de 30 % supérieure à celle qui est indiquée par des calculs basés sur l'hypothèse d'une distribution homogène de l'isotope dans le parenchyme rénal.

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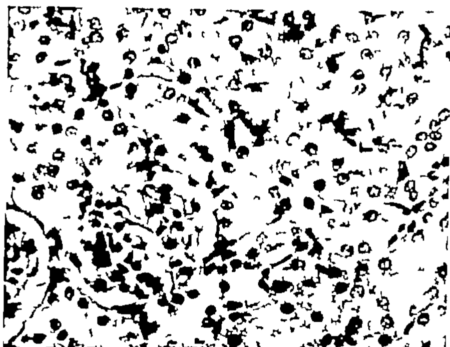


Fig. 4. High-resolution autoradiogram of the same kidney as in fig. 3 reveals that the silver granules lie above the tubular cells.

tope is retained in the medulla. The ratio of the cortical parenchyma to that of the medulla in human kidneys is 259/100 (HOLLATZ 1922). Furthermore, as it was shown that most of the radioisotope was accumulated in the distal convoluted tubules, the radiation doses will be even greater for these than for other parts of cortex. The radiation dose for kidneys with Neohydrin $^{203}$Hg has been calculated on the assumption that the tracer substance is evenly distributed in the renal parenchyma (SELTZER et coll. 1964), but as the present studies have revealed that the isotope is accumulated in the cortex, the radiation dosage in this area will be at least 30 % greater.

The localization of Neohydrin $^{203}$Hg in the renal cortex is identical to that reported in the studies on the localization of radiocobalt ([illegible]Co) in rat kidney (KASANEN et coll. 1964, LINDGREN & SALMI 1964).

## SUMMARY

The distribution of radioactive Neohydrin $^{203}$Hg has been studied in rat kidney by autoradiography and scintillometric measurements. The radioactivity accumulated rapidly in kidney tissue and was located solely in the cortex, mainly in the distal convoluted tubules. The radiation dose to the cortex is therefore at least 30 % greater than that obtained from calculations based on the assumption that the isotope is evenly distributed in the renal parenchyma.

Nuclear or elementary particle reactions do not occur in connection with such radiation qualities as are used in roentgendiagnostic examinations. Then most of the energy imparted will be degraded and ultimately appear as heat. Some of it, however may appear as a change in interatomic bond energies. If the irradiated matter is an element or even pure water the energy that appears as changes in the chemical bond energies may be neglected and the energy imparted to a specified and isolated mass may be equated to the heat increase in this mass. Even the heat loss by thermal radiation must be negligible. The integral absorbed dose in the whole body (for short integral dose) in a roentgendiagnostic examination is as a rule less than 1 J = 10 erg = 100 kg rad. An integral dose of 100 kg rad causes an average temperature enhancement in a patient of as little as 3 10 degrees. This measure is much too small to be detectable in man

The integral dose is nearly proportional to the radiation energy incident on the patient. This radiation energy may be measured by a detector that totally absorbs the radiation. Of course such a measurement can not be performed simultaneously with the use of the radiation for a roentgendiagnostic examination. In measurements of the integral dose in routine roentgendiagnostic examinations the detector must not disturb the examination

Feddema & Oosterkamp (1953) measured the product of beam area and irradiation time during fluoroscopy using a kWh meter connected to the adjustable diaphragm of the roentgen unit via potentiometers and cog wheels. For all the radiation qualities used, they measured central-axis depth doses in a water tank irradiated by a beam with a very large cross section. The integral doses could then be calculated from the measured product of field area and irradiation time when the current and voltage in the roentgen tube are known. In an earlier article (Carlsson 1963) the author discussed methods and gave data for calculating the integral doses when the exposure in air and the field area were known

As the exposure in air $X$ varies over the area $A$ a determination of $\int XdA$ (the areal exposure) is better than a single measurement of the exposure in the central ray. The quantity $\int_A XdA$ is independent of the distance to the radiation source over distances permitting the attenuation of radiation to be neglected, and when the scattered radiation from the environment is negligible. The area, $A$ is measured in a plane perpendicular to the central ray and the exposure $X$ is determined in the same plane

A large air-equivalent plane-parallel ionization chamber a monitor mounted on a roentgen apparatus between the adjustable diaphragm and the patient, measures $\int XdA$ (Fig 1). The area of the monitor must be larger than the maximal beam cross section. The monitor serves then as an added

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# INTEGRAL ABSORBED DOSES IN ROENTGEN DIAGNOSTIC PROCEDURES

## I. The dosemeter

by

CARL CARLSSON

The following definition of *energy imparted* to matter is given in the ICRU Report 10a:

The *energy imparted* by ionizing radiation to the matter in a volume is the difference between the sum of the energies of all the directly and indirectly ionizing particles which have entered the volume and the sum of the energies of all those which have left it, minus the energy equivalent of any increase in rest mass that took place in nuclear or elementary particle reactions within the volume.

The *integral absorbed dose* in a certain volume, according to MAYNEORD (1940), may be defined as the mass integral of the absorbed dose integrated over the volume.

The quantities energy imparted to a volume and integral absorbed dose in the same volume are quite identical. Calculations and measurements of the integral absorbed dose according to both definitions have been discussed in a previous paper (CARLSSON 1963).

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Nuclear or elementary particle reactions do not occur in connection with such radiation qualities as are used in roentgendiagnostic examinations. Then most of the energy imparted will be degraded and ultimately appear as heat. Some of it, however, may appear as a change in interatomic bond energies. If the irradiated matter is an element or even pure water, the energy that appears as changes in the chemical bond energies may be neglected and the energy imparted to a specified and isolated mass may be equated to the heat increase in this mass. Even the heat loss by thermal radiation must be negligible. The integral absorbed dose in the whole body (for short integral dose) in a roentgendiagnostic examination is as a rule less than 1 J = 10 erg = 100 kg rad. An integral dose of 100 kg rad causes an average temperature enhancement in a patient of as little as 3 10 degrees. This measure is much too small to be detectable in man.

The integral dose is nearly proportional to the radiation energy incident on the patient. This radiation energy may be measured by a detector that totally absorbs the radiation. Of course such a measurement can not be performed simultaneously with the use of the radiation for a roentgendiagnostic examination. In measurements of the integral dose in routine roentgendiagnostic examinations the detector must not disturb the examination.

FEDDEMA & OOSTERKAMP (1953) measured the product of beam area and irradiation time during fluoroscopy using a kWh-meter connected to the adjustable diaphragm of the roentgen unit via potentiometers and cog wheels. For all the radiation qualities used, they measured central-axis depth doses in a water tank irradiated by a beam with a very large cross section. The integral doses could then be calculated from the measured product of field area and irradiation time when the current and voltage in the roentgen tube are known. In an earlier article (CARLSSON 1963) the author discussed methods and gave data for calculating the integral doses when the exposure in air and the field area were known.

As the exposure in air, $X$, varies over the area, $A$, a determination of $\int XdA$ (the areal exposure) is better than a single measurement of the exposure in the central ray. The quantity $\int XdA$ is independent of the distance to the radiation source over distances permitting the attenuation of radiation to be neglected, and when the scattered radiation from the environment is negligible. The area, $A$, is measured in a plane perpendicular to the central ray and the exposure $X$ is determined in the same plane.

A large air-equivalent plane parallel ionization chamber, a monitor mounted on a roentgen apparatus between the adjustable diaphragm and the patient, measures $\int_A XdA$ (Fig. 1). The area of the monitor must be larger than the maximal beam cross section. The monitor serves then as an added

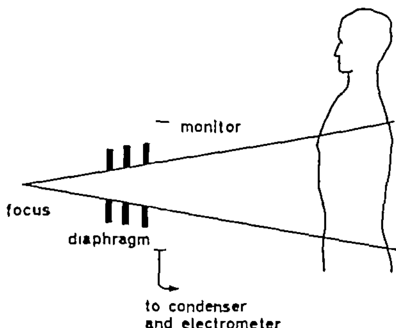



Fig 1 Schematic drawi g showing th measuring principle.

filter slightly changing the primary spectrum and reducing the exposure rate The reduction of the exposure rate caused by the monitor here described is about 15 % depending to some extent on the radiation quality

Monitors of this type have been described by AIRTH 1959 1964 CARLSSON & LIDÉN 1959a NEBOSCHEW & SCHOTT 1959 REINSMA 1959 1960 1960—62 GOLDMAN LORENZ & WOLF 1960 ZIELER 1960 1961 1964 ARNAL & PYCHLAU 1961—62 MORGAN 1961 1964 PYCHLAU & PYCHLAU 1964 The monitor does not disturb the examination except in the case of roentgen installations with beam illumination In this case the monitor has to be removed when directing the beam for example, by means of hinges MORGAN as well as PYCHLAU & PYCHLAU have avoided this trouble by constructing transparent monitors.

The current from the monitor usually charges a condenser the voltage of which is measured by an electrometer

The equipment used in the present integral dose measurements will be described in the following sections.

## Measuring equipment

*The plane parallel ionization chamber (the monitor)* The outer dimensions of the monitor are 23 × 23 × 1 4 cm³ or in some cases 17 × 17 × 1 4 cm³ (Fig 2) The square cross-section of the active volume of the monitor is larger than the

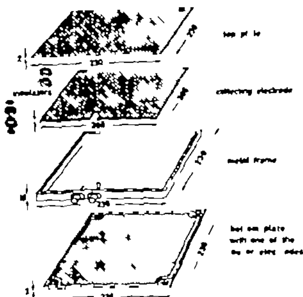



Fig. 2. Exploded view of the monitor. The dimensions are given in mm.

maximal cross-section of the beam passing the monitor. Its collection electrode is made of 2 mm thick graphite-coated perspex. The polarization electrodes consist of graphite layers on the inner side of 2 mm thick perspex plates. The plates are coated with graphite also on the outer surfaces. These graphite layers are connected to earth in order to make the outside of the monitor electrically neutral and to serve as an electrostatic shield. The insulators, which are made of polyethylene, also define the distance (4 mm) between the electrodes. The leakage current over the four insulators is reduced by leading it to earth. To avoid short-circuiting of the monitor by dust from the graphite coating, the graphite layers are flamed and polished.

*Recombination of ion pairs.* The positive and negative ions created in an irradiated ionization chamber would ultimately recombine if there were no electrostatic field in the chamber.

Some of the ions recombine in the ion clusters in which they are created (initial recombination), others when moving towards the electrodes (general recombination).

The initial recombination is independent of the exposure rate. Hence an ionization chamber with high initial recombination, if calibrated against an

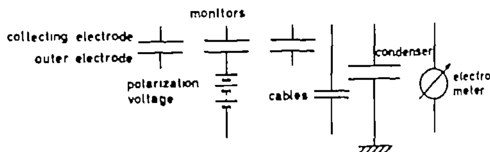



Fig. 3. The measurement circuit.

ionization chamber without this drawback accurately measures the exposure if the radiation qualities and the geometry are unchanged.

For small values of the linear energy transfer as for roentgen radiation in air at atmospheric pressure, the initial recombination is negligible.

The general recombination increases with increasing exposure rate and electrode distance and decreases with increasing field strength. The general recombination in the monitor has been calculated according to Boag.

A constant voltage of 300 V is used for the polarization which gives a field strength of 300/0.4 = 750 V/cm. As the voltage over the condenser as a rule is less than 3 V and never more than 10 V the field strength is practically constant during a measurement. The maximal measured exposure rate to which the monitor is exposed with the roentgen units used in this examination is about 60 R/s. As both current and voltage of the roentgen tubes are pulsating the exposure rate is higher than the measured time average value when voltage and current are maximal. The voltage and current of those tubes with the highest exposure rate have however very small ripples owing to a 12 pulse rectification. The voltage ripple in these tubes is not more than 5 %. As an exposure rate of about 600 R/s is necessary to cause a general recombination of 1 % in the monitor this effect is totally negligible.

*The electrometer.* The electrometer used is an ultra high impedance d.c. voltmeter with full scale range of 0.03, 0.10, 0.30, 1.0, 3.0, 10, 30 and 100 V. The input resistance is greater than $10^{1}$ ohm shunted by 25 pF. The accuracy is within 2 % of full scale on all ranges.

The adjacent ranges make it possible to choose a suitable range for integral dose measurements for any type of roentgendiagnostic examination.

*The condenser and connections.* The current from the monitor charges a high insulating styrene condenser. The capacitance of the condenser 0.5 μF is large compared to other connected capacitances: the monitor 200 pF, the cable 80 pF/m and the electrometer 25 pF.

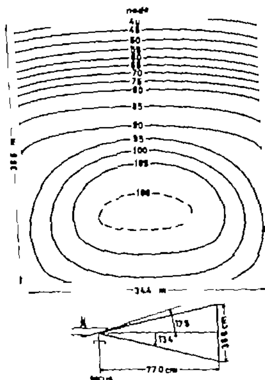



Fig. 4 Measured iso-exposure curves in air from diagnostic roentgen tube 75 kV and HVT = 4.5 mm Al.

The condenser and the electrometer are placed in the control room and connected to the monitors by means of noise-free coaxial cables. Each roentgen tube in the examination room is equipped with a monitor All the monitors are connected in parallel to the same electrometer (Fig 3) This is possible as only one tube is used at a time.

In different examination rooms the number of monitors can vary between 1 and 4 and the cable length between 6 m and 50 m. The maximal capacitance of cables, monitors and electrometer is then less than 5 000 pF i. e. less than 1 of the capacitance of the condenser The calibration of one monitor is therefore valid even if more monitors are connected to the same electrometer

## Calibration of the monitors

*Calibration for ∫ XdA (areal exposure)* The calibration of the monitors in units of R cm /A was performed with a substandard ionization chamber of thimble type connected to a vibrating reed electrometer The substandard

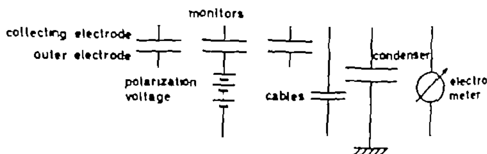



Fig 3 The measurement circuit

ionization chamber without this drawback accurately measures the exposure if the radiation qualities and the geometry are unchanged

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*The electrometer* The electrometer used is an ultra high impedance d c. voltmeter with full-scale range of 0.03 0.10 0.30 1.0 3.0 10 30 and 100 V The input resistance is greater than $10^{14}$ ohm shunted by 25 pF The accuracy is within 2 % of full scale on all ranges

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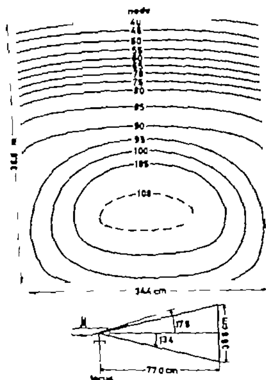



Fig. 4 Measured iso-exposure curves in air from diagnostic roentgen tube; 75 kV and HVT = 4.3 mm AL

The condenser and the electrometer are placed in the control room and connected to the monitors by means of noise free coaxial cables. Each roentgen tube in the examination room is equipped with a monitor All the monitors are connected in parallel to the same electrometer (Fig 3) This is possible as only one tube is used at a time

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## Calibration of the monitors

*Calibration for ∫ YdA (areal exposure)* The calibration of the monitors in units of R cm /V was performed with a substandard ionization chamber of thimble type connected to a vibrating reed electrometer The substandard

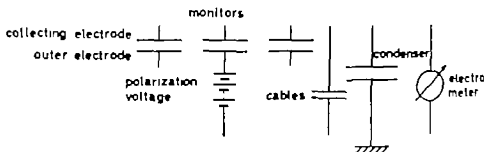



Fig 5 The measurement circuit.

ionization chamber without this drawback accurately measures the exposure if the radiation qualities and the geometry are unchanged

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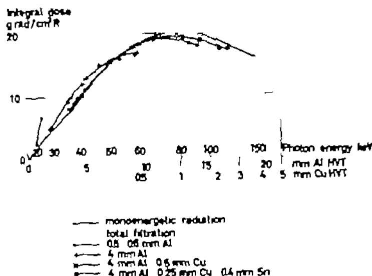



Fig. 6. Integral doses per cm² and R in 20 cm thick water slab as function of radiation quality

*Comparison of different monitors.* The response of the different monitors used in the integral dose measurements was tested with identical geometry and various radiation qualities. The differences from a common average value were less than 3 % at HVT:s from 3.4 to 6 mm Al, which in routine measurements was considered good enough to justify the use of a common calibration curve for all the monitors.

*Calibration for integral dose.* Measured value of the areal exposure can be transformed to integral dose according to a method published earlier (CARLSSON 1963). In that work the incident energy per cm² and roentgen is determined from known primary spectra; the integral dose is then obtained by subtracting the escape energy (transmission and reflection). In Fig. 6 an example valid for a 20 cm thick patient is given. The integral dose, as shown in Fig. 6, is no unequivocal function of the HVT of the radiation. It varies with the total filtration of the roentgen tube; hence the total filtration has been determined for each roentgen apparatus used in this examination.

*Total filtration.* By total filtration is meant the sum of the inherent and added filtration. For diagnostic roentgen tubes the inherent filtration usually is given in terms of an equivalent thickness of aluminium. This equivalence of

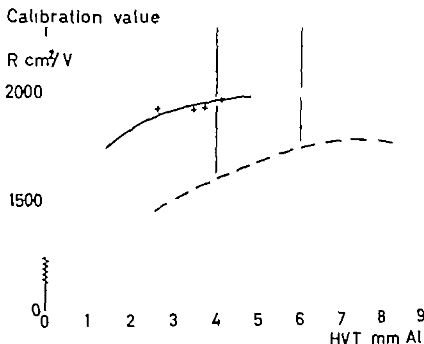



Fig 5 Calibration values in units of R cm²/V of the monitors as a function of HVT Solid line without and dotted line with couch (table top) between monitor and patient The crosses show calibration values determined by means of iso-exposure curves, as in fig 4

chamber was placed in free air at a distance from the focus corresponding in most cases to focus patient distance The substandard chamber was then irradiated by radiation transmitted by the monitor The calibrated monitor then measures the radiation being transmitted by the monitor itself

On two roentgen units with multiplane diaphragms $\int_A I dA$ was measured at four radiation qualities The angle of aperture of the beam was rather great, approximately 16 and 25 With the monitor in place, and by means of the substandard chamber iso-exposure curves were determined from which the areal exposure and the calibration value of the monitor could be calculated in units of R cm²/V One example from the iso-exposure measurements is shown in Fig 4

The variation of the calibration value with radiation quality was more thoroughly examined with a smaller field the exposure being determined in the central ray only The calibration values of the monitors as a function of the HVT of the radiation are given in Fig 5 The softer the radiation quality the smaller the calibration value — that is, the less of the radiation registered by the monitor will reach the patient. This energy dependence is most marked with a table top between monitor and patient (Fig 5)

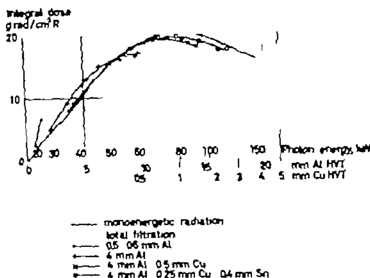



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Fig. 7. HVT as a function of the tube voltage of one of the diagnostic roentgen tubes. Symbols × roentgenography + fluoroscopy

the filter can be determined from measurements of the ability (1) to reduce the exposure rate or (2) which is used here to change the HVT of the radiation — that is to change the spectrum. Data published by REINSMA 1960 have been used for the determination of the equivalent aluminium thickness of the total filtration. They give the total filtration as functions of HVT, voltage and wave form. The aluminium equivalence of a filter varies with the tube voltage if the atomic number of the filter material differs from that of aluminium. Thus the contribution of the monitor to the total filtration varies with the tube voltage as the material in the monitor has an effective atomic number of approximately 6.

*HVT measurements.* In order to use the calibration data in Figs 5 and 6 together with the data for determination of the total filtration which are all expressed as functions of the HVT in mm Al, the HVT has been measured in narrow beam geometry for all the roentgen tubes used. Then the plane-parallel ionization chamber served both as monitor and filter. HVT as a function of the voltage for one roentgen tube is shown in Fig. 7. The HVT or HVL is defined as that thickness of material which reduces the exposure rate from the primary radiation to one half.

## Recording

For routine measurements of integral doses a digital record of the measured value is to be preferred instead of reading off a dial instrument (MORGAN 1961).

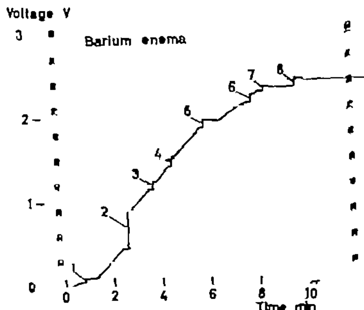



Fig. 8. Record of colon examination. The sloping lines indicate fluoroscopy vertical lines roentgenography and horizontal lines that the roentgen tube switched off.

as it is easier to handle and has a measuring range of several decades. However some of the digital voltmeters are too slow for proper registration of events as swift as radiographic procedures (BERGER & FURNAGEL)

By connecting a recorder to the electrometer the administration of the irradiation as a function of time can be studied. An example of recording in a colon examination is shown in Fig 8. A period of fluoroscopy (low exposure rate) is recorded as a sloping line whose gradient increases with field area, tube voltage and tube current (kV and mA) Roentgenograms (high exposure rate) are recorded as vertical lines, whereas horizontal lines on the record mean that the tube is switched off At the end of the examination the condenser is discharged and the instrument is ready for a new measurement. Preliminary reports on the records were published in 1961 and 1962. Similar records are reported by AIRTH.

It is possible to calculate from a record the integral dose from known voltage data for the roentgen tube during the different examination moments. Besides the obvious possibility to determine the integral dose at the different examination moments, the record also shows such details as the time of fluoroscopy and the technique used by the examiner

**Energy independent monitors for integral dose measurements**

The monitor described here is approximately energy independent in measuring the areal exposure ($\int_A X dA$) (Fig 5)

The integral dose per cm and roentgen unit increases with increasing voltage of the roentgen tube i e with harder radiation quality (Fig 6) The calculation of integral doses from the records of a roentgendiagnostic examination is then a rather time-consuming process which could be saved by using a monitor that is energy independent for integral dose measurements.

If the electrodes of an ionization chamber are coated with very thin metal layers the energy dependence of the ionization chamber for exposure measurement can be varied within wide limits by varying the metal (atomic number) the thickness of the layer and the electrode distance (EBERHARDT & JAEGER) A proper choice of these three variables may produce energy independence for integral dose measurements at least with a certain filtration of the roentgen tube (Fig 6) Our experiments in constructing ionization chambers of non air-equivalent material resulted in small ionization chambers with a great sensitivity and a good energy independence for exposure measurements between HVT 2 5 to 8 mm Al (CARLSSON & LIDÉN 1959b) The attempts to construct a monitor that is energy independent for integral dose measurements were abandoned owing to the complexity of the energy dependence (Fig 6)

REINSMA (1962) avoided the work of calculating the integral dose from the measurements in the following three ways

1 By correcting electrically the measured value of the areal exposure to the integral dose the correction is thereby guided by the voltage of the roentgen tube

2 By constructing a monitor with electrodes of thin gold layers the desired energy dependence is attained as discussed above

3 By means of a dual monitor the two monitors are separated by a filter and the electrometer measures the difference between the ionization currents of the two chambers by suitable selection of material and thickness of the filter and varying the electrode distance in both monitors the energy dependence desired is reached

MORGAN attained the desired energy dependence in a dual monitor by decreasing the sensitivity for low energy photons by using a copper filter and ethane gas in the monitor

Both REINSMA and MORGAN measure the incident energy Deviations in the measurements of integral dose by REINSMA and others, from those presented here have been discussed earlier (CARLSSON 1963)

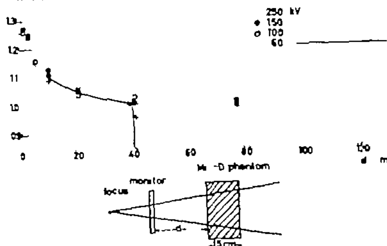



Fig. 9. Relative overestimation of the integral dose due to scattered radiation from the patient (detected by the monitor) as function of the distance between monitor and patient.

## Accuracy of the method

In *the ∫ XdA-calibration* the monitor will register both the off focus radiation and the radiation scattered in tube house which do not reach the area of the iso-exposure measurement (or the patient) The amount of off-focus radiation varies with the type of diaphragm. When the chamber is used with a single diaphragm (shutter blades in one plane only) the monitor gives a higher response for the same integral dose than when the chamber is used with a series of diaphragms in different planes. As the monitors are calibrated together with diaphragms in three planes, the integral dose will be overestimated when the monitors are used with simpler diaphragms and underestimated when in perfect collimation

*Sensitivity to scattered radiation* As the monitor has a larger cross section than the primary beam, it is very sensitive to scattered radiation The distance between the patient and the monitor will then affect the measurements. The results from an investigation of this effect, using a mix D phantom at various distances from the monitor are given in Fig 9 As the calibration is performed without scattering media in the proximity of the monitor and the substandard chamber the integral dose will be overestimated when the patient is close to the monitor According to Fig 9 this overestimation, which is somewhat dependent on the beam cross-section, amounts to about 10 % for a patient monitor distance of 10 cm.

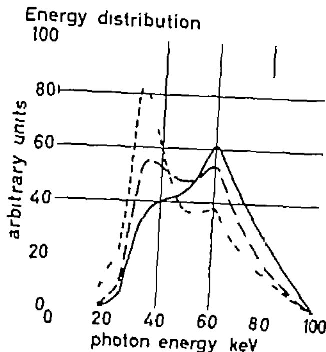



Fig 10. Energy distributions of exposure ( ) particle fluence (— — —) and energy fluence (———) for 100 kV radiation with a total filtration equivalent to 4 mm AL. The spectra are normalized to the same area.

*Calibration for integral dose* The accuracy of the method of transforming areal exposure to integral dose is difficult to estimate The method is based on measured spectra from which the exposure in air and the incident energy per unit area are calculated as functions of the photon energy Fig 10 shows exposure spectrum number spectrum and energy spectrum for 100 kV radiation with a total filtration equivalent of 4 mm Al The measured number spectra are most uncertain at low photon energies owing to the decreasing energy resolution of the NaI(Tl) spectrometer with decreasing photon energy corresponding to photo peak half widths of 9 6 % at 279 keV 16 % at 81 keV (HETTINGER & STARFELT 1958) and perhaps as poor as 25 % at 25 keV This fact does not seriously affect the determination of the incident energy but the exposure is more sensitive to an inaccurate number of low energy photons as the exposure per photon in air decreases rapidly with increasing photon energy in the region under 30 keV

The harder the filtration the less numerous are the low-energy photons in the spectra resulting in more accurate calculations of the integral dose from measurements of the areal exposure

The accuracy in the values given in Fig 6 is presumably better than ± 20 % if the total filtration is equivalent to 4 mm Al or more The accuracy in measurements of the integral dose in a water slab would then be as good as ± 25 % in most cases In routine measurements of integral doses in patients, the accuracy is still lower Some factors influencing this accuracy are given below

*Radiation passing outside the patient* is registered by the monitor and causes overestimation of the integral dose. This overestimation is especially marked in roentgendiagnostic examinations of the extremities, and the head and neck and is also of importance in examinations of the lungs but may be neglected in examinations of the gastrointestinal tract.

The *neglect of side scatter* when considering the patient to be equivalent to an equally thick water slab with infinite lateral extent, is generally of small importance (CARLSSON 1963) This phenomenon may be explained by the fact that the number of photons scattered per solid angle for photon energies is minimal at an angle of 90

The minimum escape energy in lateral direction can be derived from measurements of the energy and angular distribution of roentgen radiation in a water tank (HETTINGER & STARFELT 1959 HETTINGER & LIDÉN 1960) Determinations of the angular distribution of (1) the exposure of the radiation scattered from a tissue-equivalent mix D phantom (30 × 30 × 22 cm³) (BOMFORD & BURLIN) and (2) the escape energy from a man-equivalent Alderson phantom (BONDE) support the statement by the author (CARLSSON 1963) that the overestimation of the integral dose by neglecting side scatter will be less than 8 %

For the varying thickness of a given patient in different directions — or of different patients — no exact correction can be made in practice. The average thickness of the trunk of adult patients in antero-posterior direction is about 20 cm. If in the integral dose measurements all patients are assumed to be 20 cm thick, the integral dose for a 15 cm thick patient will be overestimated by 8 to 16 % and underestimated for a 25 cm thick patient by 2 to 9 % (higher values for harder radiation qualities) (CARLSSON 1963)

*Inhomogeneities in the body* such as bones, appreciably affect the distribution of the absorbed dose but have a negligible influence upon the integral dose. A small overestimation of the integral dose will be made assuming the energy absorbed by high-contrast media as integral dose to the patient.

*Variations in temperature and atmospheric pressure* cause changes in the sensitivity of the monitor which ought to be corrected for by means of the gas law The temperature in the examination room does not vary more than about ± 2 degrees. The temperature of a roentgen tube in frequent use will however rise appreciably and warm up the monitor A measurement of the temperature enhancement of the monitor situated on one of the roentgen units in most frequent use (a universal stand) resulted in an increase of 3.4 degrees in 2.5 hours This temperature difference causes a sensitivity change of about 1 % in the monitor

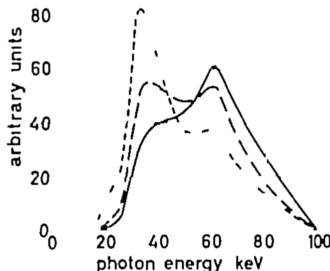



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## RÉSUMÉ

Description de chambres d'ionisation à électrodes planes parallèles et de circuit de mesure pour la mesure et l'inscription des doses intégrales reçues au cours des examens radiologiques. Description détaillée de l'étalonnage de ces dosimètres et étude de leur précision. Les enregistrements obtenus permettent une étude approfondie de la part qui revient dans la dose intégrale à chaque phase de l'examen.

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The range of atmospheric pressure variations during a year is usually between 735 and 780 mm Hg causing a sensitivity variation of the monitor that will not exceed 3 %. Hence in the measurements of integral doses, corrections according to the gas law have been neglected.

*Double registration.* As there are sometimes several monitors in the same examination room and as all of them are continually ready for measurement, even the monitors not situated on the used roentgen tube may contribute to the measured value. This risk seems especially great with monitors mounted on the tubes over and under the same couch, but since in this case either the Potter grid and lead backed film cassette or the fluorescent screen backed with lead glass are in the beam together with the patient, the contributions to the measured value from the monitors not directly irradiated are negligible.

## Conclusions

Measurement with a plane parallel ionization chamber (a monitor) is a useful method for determining integral doses. The mapping of the roentgen examinations by the method described above may also be used for simulating these examinations when irradiating phantoms in which special dose measurements (gonad dose, bone marrow-dose) are performed which cannot be carried out on patients or which seriously disturb the examination.

## Acknowledgements

I wish to express my sincere gratitude to Dr Jan Cederlund, who as early as 1957 gave me the idea to construct the plane-parallel ionization chamber, and to Professors Kurt Lidén and Olle Olsson for valuable discussions and continual encouragement. The investigation was supported by grants from the Swedish Cancer Society and the Swedish Medical Research Council.

## SUMMARY

Plane parallel ionization chambers (monitors) and a suitable electrometer circuit for the measurement and recording of integral doses in roentgen-diagnostic examinations are described. The calibration of the monitors is described in detail and the accuracy discussed. The records obtained permit a careful analysis of the contribution to the integral dose from every moment of the examination.

## ZUSAMMENFASSUNG

Planparallelle Ionisationskammern (Monitore) und eine geeignete elektrometrische Anordnung für die Messung und Aufzeichnung von Integraldosen bei röntgendiagnostischen Untersuchungen werden beschrieben. Die Kalibrierung der Monitore wird im Detail beschrieben und die Genauigkeit diskutiert. Die erhaltenen Aufzeichnungen gestatten eine sorgfältige Analyse der Verteilung der Integraldosis zu jedem Zeitpunkt der Untersuchung.

## RÉSUMÉ

Description de chambres d ionisation à électrodes planes parallèles et de circuit de mesure pour la mesure et l'inscription des doses intégrales reçues au cours des examens radiologiques. Description détaillée de l'étalonnage d ces dosimètres et étude de leur précision. Les enregistrements obtenus permettent une étude pprofondie de la part qui revient dans la dose intégrale à chaque phase de l'examen.

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## Books received

We acknowledge with thanks under this heading books received for review; we trust this will be regarded as a sufficient mark of appreciation of the courtesy of the sender. Reviews of selected items will appear as soon as an opportunity affords.

CELLULAR RADIATION BIOLOGY. A SYMPOSIUM CONSIDERING RADIATION EFFECTS IN THE CELL AND POSSIBLE IMPLICATIONS FOR CANCER THERAPY. Collection of Papers presented at the 18th Annual Symposium on Fundamental Cancer Research 1964. Williams & Wilkins Co, Baltimore 1965.

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## BOOK REVIEW

MEDICAL ASPECTS OF RADIATION ACCIDENTS. A HANDBOOK FOR PHYSICIANS, HEALTH PHYSICISTS AND INDUSTRIAL HYGIENISTS. Edit. by Eugen L. Saenger U S Government Office Washington 25 D C. Price 1 75 U S dollars.

This eminently practical handbook gives, as it is stated a cookbook approach to the problems to be mastered in various cases of radiation accidents. The general features of accidents that have occurred, or may be ant cipated, are considered as a prerequisite for an understanding of the measures that should be taken, and their order of priority The radiation effects pertinent to th matter and the more important radiation survey instruments are reviewed. The contributors rightly stress the necessity for detailed preplanning jointly w th the appropriate authorities, n anticipation of any imaginable radiation accident in various medical, industrial and other establishments. A substantial part of the book is devoted to rescue organization and equipment, hospital disaster plans, decontamination procedures for victims, material and food, q estions of mass and individual psychology in disaster conditions, and public relations. This may well be the most useful one for medical and scientific readers, who may find the parts on radiation effects and measuring methods for i stance, rather elementary and at times not too accurate Much of the matter in the numerous tables may at the same time prove to be of considerable practical use.

*Sten Bauer*

# ACTA RADIOLOGICA

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Vol. 3 Fasc. 5 | New series THERAPY PHYSICS BIOLOGY | 1965 October


# CLINICAL TRIAL OF RADIOSENSITIZERS INCLUDING SYNKAVIT AND OXYGEN INHALED AT ATMOSPHERIC PRESSURE


by

J S MITCHELL, DIANA BRINKLEY and J L HAYBITTLE


This is an account of a clinical trial of radiosensitizers, which was started in February 1958. It was organized to try to reach a decision concerning the value of intravenous Synkavit, of oxygen inhaled at atmospheric pressure and of the combined use of intravenous Synkavit and oxygen inhaled at atmospheric pressure as radiosensitizers in the radiotherapy of patients with inoperable carcinoma of the bronchus. Synkavit (Roche Products) is chemically 2 methyl 1 4-naphthaquinol bis(disodium phosphate) In addition a closely related compound, 2,3-dimethyl 1 4-naphthaquinol bis(disodium phosphate) described here as compound 28 was included in this trial, because animal experiments with the Walker rat carcinoma 256 and preliminary clinical studies suggested that it might be a radiosensitizer (MITCHELL 1960)

Laboratory studies, and clinical trials of Synkavit and related compounds as chemical radiosensitizers, have been in progress in Cambridge since 1946. Detailed accounts of this work have been published (MITCHELL 1953 1960 MARRIAN MARSHALL & MITCHELL 1961) and provide the evidence upon which the present trial was based. The results of an early trial of intravenous


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Submitted for publication 1 February 1965.

Synkavit as a radiosensitizer in the radiotherapy of inoperable carcinoma of the bronchus with random allocation of patients, suggested that this compound has a small and sometimes useful effect. However, this trial was open to criticism and it was considered that it is nevertheless wise to use the experience gained and carry out another trial (MITCHELL 1960, p. 160). After a number of other clinical studies and trials including a randomized pilot trial of the effects of oxygen inhaled at atmospheric pressure, the results of which were suggestive but not conclusive, it was finally decided to set up the trial which is now described.

Meanwhile, two independent accounts of the study of intravenous Synkavit as a radiosensitizer in the radiotherapy of inoperable cases of carcinoma of the bronchus were published (DEELEY 1962; KONECNY & MECHL 1962). The latter authors summarized their findings as follows: Though a small group of patients was treated, a positive effect could be proved on the tumourous focus, manifested also by a longer average survival time. More severe postradiation changes were, however, also observed, particularly the pulmonary fibrosis. For cancer at other sites, it is relevant to mention that in a randomized trial of cases of cancer of the cheek, which were regarded as usually radioresistant, SHANTA & KRISHNAMURTHI (1964) considered that intravenous Synkavit improved the results of radical radiotherapy.

It is clear that further evidence is needed. From a practical point of view, it is almost essential to investigate common types of malignant disease with a short natural history, in order to obtain a statistically significant result within a period of about 6 to 10 years. Inoperable carcinoma of the bronchus is an obvious choice for investigation. It is an extremely common type of malignant disease with a short average survival from the beginning of treatment of about 4 months in representative series of patients receiving radiotherapy at palliative levels of dose (MITCHELL 1960, p. 145); however, the variability of the course of the disease in individual patients must be emphasized. Despite advances, only a relatively small proportion of all cases of carcinoma of the bronchus are curable by surgery. Untreated patients are often very miserable. The results of treatment of inoperable cases by present methods, including radical radiotherapy, are in general poor. Nevertheless, radiotherapy often has sufficient palliative value, apart from prolongation of life per se, to justify attempts to improve this method of treatment.

## General aspects of the trial

The principles of the design and conduct of clinical trials of radiosensitizers have been discussed in some detail (MITCHELL 1960, pp. 136—166; MARRIAN, MARSHALL & MITCHELL 1961, pp. 254—263).

We felt that we had evidence that Synkavit was a radiosensitizer and that oxygen inhaled at atmospheric pressure and Compound 28 might also be radiosensitizers. Accordingly we did not feel justified in treating a group of patients with roentgen radiation only without the possible benefit of a radiosensitizer. The choice of our groups was designed to (1) re-assess the effect of Synkavit (2) assess the effect of oxygen inhaled at atmospheric pressure, and (3) assess the effect of Compound 28.

In the present trial, which was started on 11 February 1958 and finished on 31 March 1963 there was random allocation of the patients, with proper safeguards, to one of the following four groups (a) Synkavit, oxygen and roentgen therapy (abbreviated as $S + O_2 + X$) 61 cases (b) Synkavit and roentgen therapy ($S + X$) 75 cases (c) oxygen and roentgen therapy ($O + X$) 51 cases (d) Compound-28 and roentgen therapy ($28 + X$) 53 cases.

The details of the intravenous administration of the compounds, of the oxygen inhaled at atmospheric pressure, and of the radiotherapy were substantially the same as in the previous trials and will be described below. It is to be noted that the standard radiotherapy was an 8-day course of roentgen irradiation at the medium palliative level of dose.

It was intended that comparison of group (a) with group (c) would give a measure of the effect of Synkavit, while comparison of group (a) with group (b) would give a measure of the effect of oxygen. Comparison of groups (b) and (d) would give a measure of the relative effects of Synkavit and Compound 28 as radiosensitizers. Accordingly every patient in the trial received treatment which was expected to produce results which would be at least as good as those of conventional radiotherapy and probably would be appreciably better.

It was planned to continue this trial to include at least 700 patients. Only the male patients in this trial are considered. The trial was stopped after the treatment of 240 patients as soon as the results of a survey of the first 200 treated up to 1 June 1962 and assessed at 30 November 1962, became available. Among many other results, it was found that, when all patients in each group were considered, the 12 month survival rate, calculated by the actuarial method, was significantly greater with group (a) than with group (c) the difference being $= 0.168 \pm 0.077$ $P = 0.034$. It appeared that the survival in group (c) was less than in the other three groups.

Although the difficulties of stopping the trial, when a certain level of statistical significance had been reached, were fully appreciated (see ARMITAGE 1958) it was felt that the advantages of the combined treatment (Synkavit plus oxygen inhalation plus roentgen irradiation) were fairly certain and that the trial must be stopped and whenever possible, the patients should be given intravenous Synkavit and oxygen inhaled at atmospheric pressure as radio-

sensitizers This problem is a further example of the necessity of planning to depart from what may be termed the ideal form of clinical trial with deliberate sacrifice of some information in the interest of the patients

In assessing the results of the different types of treatment, it was decided that the only criterion applicable as a reliable quantitative measure was the time of survival after the first radiation treatment It must be emphasised that survival per se is not always the most important factor to be considered The benefits of palliative radiotherapy in the relief of haemoptysis and of the symptoms of superior mediastinal obstruction are to a large extent not reflected by the survival times. In the earlier clinical trial of Synkavit (MITCHELL 1960 pp 139—140 and 154—157) the use of the performance status (KARNOFSKY et coll 1951) was studied with a view to estimate the prolongation of useful life attributable to the treatment. There appeared to be a general parallelism between increased survival and prolongation of useful life and there were very few patients with long survivals at a miserable level of existence. *It was concluded that there can be little doubt, from observation* of the patients, that in many cases without evidence of extrathoracic spread treatment with roentgen therapy combined with intravenous Synkavit has been amply justified

*Details of trial* The trial was organized according to the following rules. In all cases of inoperable carcinoma of the bronchus — with the exception of cases after thoracotomy or any other form of surgery other than biopsy — as soon as the provisional diagnosis was made, the case was registered with the trial and allocated to one of the four forms of treatment, using two tables of random numbers

| *Table 1* | *Table 2* | *Treatment* |
|---|---|---|
| Even | Even | Roentgen therapy and oxygen |
| Even | Odd | Roentgen therapy and oxygen and intravenous Synkavit |
| Odd | Even | Roentgen therapy and intravenous Synkavit |
| Odd | Odd | Roentgen therapy and intravenous Compound 28 |

The oxygen was administered by inhalation at atmospheric pressure by means of either a B L B mask or plastic Polymask (British Oxygen Company No 330 216) at the rate of 8 l/min starting 20 min before and continuing throughout the whole of the irradiation on each day of treatment.

The intravenous injections of Synkavit and Compound 28 were started as soon as possible after allocation of the type of treatment, and every endeavour was made to reach as high a dose of the compound as possible or as tolerated. If there was an undesirable reaction to the intravenous injections, the dose was reduced temporarily and then increased slowly

The injections of Synkavit were given 30 min before starting the roentgen irradiation on each day of treatment and where possible injections were started 3 to 5 days before treatment.

For Compound-28, tetra-sodium 2 3-dimethyl 1 4-naphthahydroquinone diphosphate, the aim was to give the intravenous injection within 5 min before starting treatment on each day

If there were medical contra indications to intravenous Synkavit or Compound-28 (for example, cerebral metastases, severe myocardial degeneration, more than minimal superior mediastinal obstruction, laryngeal obstruction or impossible veins) or to the administration of oxygen, the case was classified according to the treatment corresponding to the random numbers, even though it may have been decided that some alternative form of treatment should be given.

If, for any reason it was considered that an alternative form of treatment was desirable, this was used and noted, but the form of treatment from the point of view of assessment remained as allocated.

For the intravenous injections of Synkavit, the dosage was started usually with 75 mg and increased daily in steps of 25 mg If any undesirable reaction such as excessive coughing, nausea, faintness or discomfort, or pain in the chest, was observed after the intravenous injection, the dose was reduced to a level at which there was no such reaction and then cautiously increased again on the following days, usually by steps of 25 mg but sometimes by steps of 10 mg For most patients, the best maximum daily dose appears to be 100 mg many tolerate 150 mg and a few will tolerate 200 mg or even 250 mg With regard to the timing (which appears to be rather critical) in this trial, the injections have been given as closely as possible to 30 min before starting the roentgen irradiation on each day the rule has been interpreted as meaning 30 ± 5 min and the exact times have been noted

With Compound-28 although the timing was different, the dosage scheme was the same as that with Synkavit, although the upper limit reached with Compound 28 appears to have been 150 mg on any one day

It must be emphasized that careful arrangements were made to prevent the doctor in charge of the patient from knowing the type of radiosensitization allocated.

In this trial, every endeavour was made to employ the normal methods of

sensitizers. This problem is a further example of the necessity of planning to depart from what may be termed the ideal form of clinical trial, with deliberate sacrifice of some information in the interest of the patients.

In assessing the results of the different types of treatment, it was decided that the only criterion applicable as a reliable quantitative measure was the time of survival after the first radiation treatment. It must be emphasised that survival per se is not always the most important factor to be considered. The benefits of palliative radiotherapy in the relief of haemoptysis and of the symptoms of superior mediastinal obstruction are to a large extent not reflected by the survival times. In the earlier clinical trial of Synkavit (MITCHELL 1960, pp. 139—140 and 154—157), the use of the performance status (KARNOFSKY et coll. 1951) was studied with a view to estimate the prolongation of useful life attributable to the treatment. There appeared to be a general parallelism between increased survival and prolongation of useful life, and there were very few patients with long survivals at a miserable level of existence. It was concluded that there can be little doubt, from observation of the patients, that in many cases without evidence of extrathoracic spread, treatment with roentgen therapy combined with intravenous Synkavit has been amply justified.

*Details of trial.* The trial was organized according to the following rules. In all cases of inoperable carcinoma of the bronchus — with the exception of cases after thoracotomy or any other form of surgery other than biopsy — as soon as the provisional diagnosis was made, the case was registered with the trial and allocated to one of the four forms of treatment, using two tables of random numbers.

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in 8 fractions in an overall time of 11 days. In some patients with extrathoracic spread it was necessary to treat additional extrathoracic areas however the doses delivered to these supplementary fields are not immediately relevant to the central tumour dose delivered by the anterior and posterior thoracic fields.

The mean values of the central tumour dose and the overall time of roentgen therapy in all the histologically verified cases in the four treatment groups, are given in Table 1 together with the values, with exclusion of the cases with incomplete treatment (see below) The differences between the mean values of the central tumour dose for the four treatment groups must be regarded as within the range of the experimental error and not of statistical significance. It is interesting to note that the mean overall time is appreciably greater than the time of 8 days recommended for the standard technique, while the mean cental tumour dose for all groups is remarkably close to the recommended dose of 1 750 R.

The general organization and conduct of the trial presented considerable practical difficulties, which appear to be almost unavoidable in a busy radiotherapeutic centre. From experience of previous trials, it was decided that patients must be registered with the trial as soon as the provisional and plausible clinical diagnosis of inoperable carcinoma of the bronchus was reached after the first visit or admission of the patient to Cambridge. Many of the patients were referred from hospitals in the East Anglian Region It was often necessary to start treatment before all the histologic evidence was available. A tremendous effort has been made as far as possible to establish a diagnosis with histologic verification. However at the final assessment, only 155 cases out of the total number of 240 i. e. 64 6 % were acceptable as cases of carcinoma of the bronchus with histologic verification.

We have followed the histologic criteria for classification of carcinoma of the lung and bronchus utilized by Dr G A. Gresham, University Morbid Anatomist Cambridge. This classification divides these carcinomas into the following groups (1) squamous, (2) anaplastic, oat-celled or spheroidal-celled, 3) respiratory epithelial, (4) cubical and columnar-celled including adenocarcinoma and (5) others.

However the main problem is to obtain a definite diagnosis of carcinoma of the bronchus. In the earlier trial, MITCHELL (1960 pp 152—153) it was found that among 157 male cases with a plausible original clinical diagnosis of inoperable carcinoma of the bronchus, not technically operable or treated surgically the diagnosis must be regarded ultimately as unproved, unlikely or disproved in 22 cases, i. e. in 14 0 %. In the present trial there were no cases that were regarded as technically operable, and a substantial proportion were

**Table 1**

*Mean values of the central tumour dose and overall time of roentgen therapy in all the histologically verified cases in the four treatment groups*

(Numbers in brackets and the corresponding values of the mean central tumour dose refer to the groups after exclusion of cases with incomplete treatment i.e. after exclusion of cases receiving a central tumour dose less than 1 500 R and/or less than a total amount of 200 mg of Synkavit or Compound 28 and/or oxygen on less than two treatment days.)

| Group | Treatment | Number of cases | Mean central tumour dose (R) | Mean overall time (days) |
|---|---|---|---|---|
| a | S + O + X | 42 (40) | 1 780 (1 810) | 9.48 |
| b | S + X | 47 (38) | 1 720 (1 840) | 9.29 |
| c | O + X | 31 (28) | 1 610 (1 780) | 9.61 |
| d | 28 + X | 32 (26) | 1 720 (1 850) | 9.40 |

roentgen therapy in use in the Radiotherapeutic Centre Addenbrooke's Hospital Cambridge and to avoid any modification of the techniques as a result of the use of the radiosensitizers The radiotherapy has been of conventional type using filtered 220 or 250 kV roentgen radiation HVL 1.5 mm copper usually with 50 cm FSD and in most cases with radiographic checking of the field positions. In all cases only palliative roentgen therapy was considered justifiable and the level of dosage corresponded to medium palliation with the minimum tumour dose between one third and two-thirds of the level of radical dose appropriate to the overall time of the fractionated treatment (see Mitchell 1960 pp 149 151)

The *standard technique* recommended in this trial was with two 15 × 15 cm fields, anterior and posterior thoracic with a calculated central tumour dose of 1 750 R given in seven treatments in an overall time of 8 days. In calculating the central tumour doses by means of depth dose tables, no air or bone corrections were made

It was inevitable that the radiotherapy given should for individual patients to some extent depart from the standard technique not only because of the differences in dimension of the patients and differences in the spread of tumour but also on account of great differences in the general medical condition of the patients Within the agreed framework of trial it was necessary to allow some degree of clinical flexibility to the doctor in planning the radiotherapy

In some patients, the treatment could not be completed With a considerable number of patients, it was considered wise to increase the overall time of the radiotherapy and with some patients the central tumour dose as well as the overall time were increased to e g a central tumour dose of 2 000 R delivered

Table 3

*Male patients with diagnosis verified histologically*

| Group | Treatment | Number of cases | Survival time (from the first roentgen treatment) Log mean value | Corresponding mean survival | Variance | S.E. |
|---|---|---|---|---|---|---|
| | S + O + X | 42 | 0.7344 | 5.42 months | 0.1703 | 0 0637 |
| d | 28 + X | 32 | 0.6783 | 4 77 | 0.1223 | 0.0619 |
| b | S + X | 47 | 0.6649 | 4.62 | 0.1475 | 0.0560 |
| | O + X | 34 | 0.5758 | 3.77 | 0.1662 | 0.0700 |

The increased mean survival of 1.65 months for group ( ) in relation to group ( ) is probably significant (74 d.f. t = 1.676, P = 0 049)

Table 4

*Male patients with diagnosis verified histologically and with no evidence of extra-thoracic spread and including those with incomplete treatment*

| Group | Treatment | Number of cases | Survival time (from the first roentgen treatment) Log mean value | Corresponding mean survival | Variance | S.E. |
|---|---|---|---|---|---|---|
| b | S + X | 20 | 0.7857 | 6.11 months | 0.1054 | 0 0725 |
| | S + O + X | 32 | 0.7844 | 6.09 | 0 1498 | 0.0684 |
| d | 28 + X | 19 | 0 7412 | 5 52 | 0 1048 | 0.0744 |
| | O + X | 22 | 0.6227 | 4.20 | 0.1466 | 0.0817 |

The increased mean survival time of 1.90 months for groups ( ) and (b) combined in relation to group ( probably significant (72 d.f. = 1.693, P = 0.047)

2 Patients with incomplete treatment' are defined for this purpose as receiving a central tumour dose less than 1 500 R and/or less than a total amount of 200 mg of a radiosensitizing chemical (Synkavit or Compound-28) and/or oxygen on less that 2 treatment days.

3 All the tests of significance are one-sided. The question is asked whether the mean survival time observed with a particular radiosensitizer e. g S+ O + X exceeds the mean survival for the control group, O + X, by an exceptional amount. A decision is required only about a positive difference see e g PEARSON & HARTLEY 1954 pp 3 21 VAN DER WAERDEN 1957 pp 29—30 and 339 and Table 7)

**Table 2**

*All male patients in the trial — There are no significant differences in this table*

| Group | Treatment | Number of cases | Survival time (from the first roentgen treatment) Log mean value | Corresponding mean survival | Variance | S.E. |
|---|---|---|---|---|---|---|
| a | S + O + X | 61 | 0.6871 | 4.87 months | 0.1833 | 0.0549 |
| b | S + X | 75 | 0.6721 | 4.70 " | 0.1410 | 0.0433 |
| d | 2S + X | 53 | 0.6486 | 4.45 | 0.0890 | 0.0410 |
| c | O + X | 51 | 0.6260 | 4.28 " | 0.1361 | 0.0517 |

in a poor general condition. A number of patients referred to us for the trial were so ill that radiotherapy was not justifiable: these patients were of course not registered with the trial. There was histologic evidence that two cases were carcinoma but not of the bronchus, and in a further case at autopsy after death during the course of treatment there was no evidence of carcinoma. Very few autopsies could be obtained, largely because most of the patients died at home. The low proportion of histologically verified cases almost certainly reflects the advanced stage of disease and the pathetic state of many of the patients.

It must be mentioned that throughout the whole of this trial and during the analysis of the results, careful arrangements were made to prevent the identification of the treatment groups by anyone involved in making clinical decisions.

## Assessment of results

The criterion used for assessment of the results of the different forms of treatment is the time of survival in months from the first roentgen treatment; this is subsequently termed the survival time unless there is ambiguity. It is shown below that the length of history before treatment is not relevant.

Statistical treatment of the data is the basic necessity for assessment of the results but it is important to be cautious in making generalizations. In connection with the calculations, the following points should be noted.

1. The survival times are consistent with a log normal distribution. Accordingly, all survival times in the calculations were rounded off to the nearest half month higher than the actual survival time. The minimum survival time was therefore half a month.

increase in mean survival to 5 42 months for group (a) from 3 77 months for group (c) is probably significant at the 5 / level. The additional mean survival of 1 65 months is small but corresponds to a 44 % increase. For the same group of 155 patients, it was found that the mean length of history corresponding to the log mean values, was as follows for the four treatment groups (a) = 3 74 months, (b) = 3 07 months, (c) = 3 69 months and (d) = 4.26 months. There are no significant differences between any of these values. There is no correlation between length of history and length of survival. The length of history is almost exactly the same for groups (a) and (c) which show the greatest difference in survival. Addition of the mean lengths of history to mean survivals does not change the order of the groups in Table 3

Further evidence is presented in Table 4 which gives the mean survival times in four treatment groups for 93 male patients with the diagnosis verified histologically and with no evidence of extra-thoracic spread of the tumour and excluding those with incomplete treatment The increased mean survival of 1.90 months, corresponding to 45 % for the combined groups (a) and (b) in relation to groups (c) is probably significant at the 5 % level.

A number of negative results must be mentioned briefly No significant differences were found between the four treatment groups for the following all patients except those with incomplete treatment' all patients without extrathoracic spread, all patients with histology confirmed but excluding those with incomplete treatment or those without extra-thoracic spread, all patients with histology in groups (1) or groups (1) (2) and (3) combined. However it is of interest that in almost all these tests the lowest value of the mean survival was in group (c)

## Discussion

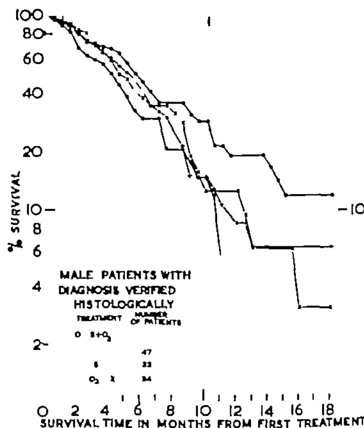
The results of this clinical trial of radiosensitizers in inoperable male cases of carcinoma of the bronchus show that in cases with the diagnosis verified histologically there is a small increase in mean survival by about 44 % for the treatment group (a) S + O + X, in relation to the treatment group (c) O — X. This increased survival is regarded as probably significant at the 5 level.

This finding and the other results summarised in Tables 2 to 4 and the Diagram suggest that

1) the radiosensitizing action of intravenous Synkavit is confirmed

2) there is no convincing evidence that under the conditions of this trial oxygen alone at atmospheric pressure is effective as a radiosensitizer and

3) Compound 28 may have a small effect as a radiosensitizer but no




Results of th clinl l trial of rad osensit zers n the treatment of i perabl carcinom of th bronchus (February 1958—March 1963) Surv val curves f r the four treatment groups for ll the male pat ents w th the diagnosis erified histolog cally

The most important results are summarised in Tables 2 to 4 and in the accompanying Diagram In the tables, the four treatment groups are arranged in order of decreasing mean survival times it is to be noted that group (c) in all the tables has the shortest mean survival time For all the 240 male patients in the trial it is clear from Table 2 that any advantages of groups (a) and (b) over (c) are very small in fact none of the differences are significant However the total of 240 patients consists of 155 with the diagnosis of carcinoma of the bronchus verified histologically together with 85 with the diagnosis unconfirmed of which in a few at least the diagnosis was proved not to be carcinoma of the bronchus

The results for the 155 male patients with the diagnosis confirmed histologically are shown in the survival curves in the Diagram and summarised in Table 3 It is interesting that in the Diagram the survival curve for group (a) is at the highest level with 19 % survival at 12 months. Table 3 shows that the

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statistically significant advantage of treatment in group (d) 28 + X over treatment in group (c) $O_2$ + X has been demonstrated.

It is concluded that intravenous Synkavit has a probably significant small, and sometimes useful, effect as a radiosensitizer.

The organization of this trial has emphasized the many practical difficulties of clinical trials and the need to introduce some degree of flexibility as an integral part of the design and conduct of clinical trials of different forms of treatment of patients with advanced malignant disease.

## Acknowledgements

We would like to acknowledge the help given to us, in the running of this trial, by the staff of the Radiotherapeutic Centre of Addenbrooke's Hospital and, in particular, the care given to the patients by the nursing staff and by the radiographers. The staff of the Records and Clerical Sections did a great deal to ensure a satisfactory follow up. We wish to thank Miss L. K. Mee for help with the calculations at an earlier stage. We would also like to thank the many surgeons and physicians who referred their patients for treatment, in particular Dr A. H. C. Couch, and Dr E. L. Brown of the West Norwich Hospital. Roche Products Ltd, Welwyn Garden City, kindly provided us with supplies of Synkavit and Compound-28 for which we are most grateful.

## SUMMARY

Description of design and conduct of a clinical trial of the radiosensitizers Synkavit, oxygen inhaled at atmospheric pressure, and a compound closely related to Synkavit in palliative radiotherapy of inoperable cases of carcinoma of the bronchus. The only conclusion which emerges from the statistical assessment of the results is that intravenous Synkavit has a small, probably significant, radiosensitizing effect.

## ZUSAMMENFASSUNG

Es wird über die Planierung und Durchführung klinischer Versuche — in der palliativen Radiotherapie des inoperablen Bronchus-Karzinoms — mit Strahlensensibilisatoren, Synkavit und bei atmosphärischem Druck eingeatmeten Sauerstoff sowie ein dem Synkavit ähnliches Präparat, berichtet. Statistisch konnte nur festgestellt werden, dass das intravenös injizierte Synkavit einen geringen, wahrscheinlich signifikanten, radiosensibilisierenden Effekt hat.

## RÉSUMÉ

Description du plan et de l'exécution d'une expérimentation clinique de radiosensibilisateurs: Synkavit, oxygène inhalé à la pression atmosphérique et un composé voisin du Synkavit, dans la radiothérapie palliative de cas inopérables de cancer bronchique. La seule conclusion qui ressorte de l'analyse statistique des résultats est que le Synkavit intraveineux a un petit effet radiosensibilisant, probablement significatif.

Fig. 1. The principle of correction by the graphical method. Percentage dose along beam axis as function of depth: curve 1 in water, curve 2 corrected according to the graphical method, curve 3 corrected for absorption differences alone.

many papers. Methods of dose planning within the chest have been reported by BURLIN (1957), DUTREIX, DUTREIX and TUBIANA (1960) and by MASSEY (1962). These methods will be dealt with under the heading Comparison with other methods of correction. Since all the methods mentioned imply calculation of the dose distribution point by point, an attempt has been made to find a less elaborate procedure even at the cost of reduced accuracy. This has resulted in a graphical method which will now be described.

*Treatment unit and measuring equipment.* The measurements described in the following were carried out with one of the ⁶⁰Co units at Radiumhemmet, an Eldorado Super G unit, manufactured by the Atomic Energy of Canada Ltd (HULTBERG et coll. 1962). This unit is equipped with a block diaphragm, with its front 35 cm from the source. The source has a diameter of 2 cm. A given field size is set by using a light beam which simulates the geometry of the gamma beam. All calculations and measurements were made at a nominal source surface distance of 80 cm.

FROM THE INSTITUTE OF RADIOPHYSICS (DIRECTOR PROF R SIEVERT) STOCKHOLM, SWEDEN

# DOSE PLANNING FOR IRRADIATION OF THORAX WITH $^{60}$Co IN FIXED BEAM TELETHERAPY

by

LENNART SUNDBOM

Attaining high accuracy in dose determination when irradiating the central parts of the thorax, involves, as is well known particular difficulties when the whole beam or part of it passes through an air filled lung The dose rate in a beam which has passed through an air filled lung can be as much as 70 % higher than the value given in the standard isodose chart obtained by measurements in water The dose increase within the lung in an individual beam may be 50 % while the total increase using an irradiation technique with two or more beams will only in exceptional cases exceed 30 %

Thus correction of the tumour dosage may easily be made with a maximum error of ± 15 % by multiplying the total dose read from standard isodose charts by the factor 1 15 as recommended by JACOBSON & KNAUER (1956) If the dose at a given point has been calculated to be 6 000 rad this range of error means that the dose actually obtained could be 5 100 rad or 6 900 rad (ignoring other sources of error) This uncertainty is relatively great and the problem of correction for an air filled lung has therefore been discussed in

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depth in the irradiated object. This procedure is practicable when the dose at a given point has to be determined. The correction factor may be expressed as

$$k_l = \frac{P_l}{P_w} = e^{\mu_w l} \qquad (1)$$

This factor increases of course, with the depth in the lung. In a water-equivalent material beyond the lung the increase continues, due to an increase in scattered radiation (BURLIN 1957). The range over which the factor $k_l$ is valid has empirically been extended beyond the lung to the distance $l/2$ where $l$ is the depth of the lung in the direction of the beam.

As can be shown very simply this is equivalent to constructing the depth dose curve for a beam by displacing all the points on the curve for water a distance equal to $l/2$, where $l$ is the distance the line has passed through the lung to the point concerned. Curve 2 in the figure is constructed in this way. Since the depth-dose curves within the central part of the beam are parallel to the curve for the beam axis the method can also be applied outside the axis.

In dose planning, this graphical method can be put into practice as follows.

1. Lines are drawn parallel to the beam axis.

2. Each of the points of intersection with the isodose curves are displaced along the actual line to an increasing depth half the total distance that the line has passed within the lungs from the entrance port of the beam to the point concerned.

To illustrate the method, an example is given in Fig. 2. Theoretically the isodose curves should be displaced along rays. However the method is only approximate and no serious error is introduced by the simplification according to point 1 (provided that the source-surface distance is not too short).

## Test of the graphical method

In order to determine the magnitude of the error introduced when using this correction method, the doses were calculated and compared with measured values for the experimental set up shown in Fig. 3. The figure shows a cross-section of the masonite phantom used.

The Bg-chambers were placed in sheets of perspex 5 mm thick. One of the sheets was placed at a depth of 240 mm in each measurement while the other sheet was at one of the depths of 60 mm, 120 mm (the position in the figure) or 180 mm. For each of these positions a varying number of masonite sheets between the phantom depths of 30 and 210 mm were replaced by sawdust. This replacement 30 mm at a time, was made both from the right to the left, and vice versa, and from the central perspex sheet outwards. The field sizes used were 7.5 × 7.5 cm and 15 × 15 cm. The values measured along the beam

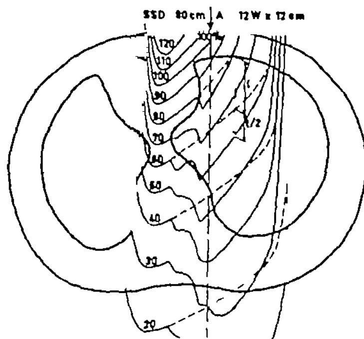



Fig. Correction of a standard isodose chart according to the graphical method. The example illustrates the method used to correct the isodose chart for a beam with wedge filter at perpendicular incidence the thorax.

The exposure measurements were made with so-called Bg-chambers. This radiation detector has been shown by SIEVERT (1934) SKÖLDBORN (1959) and by DAHL & VIKTERLÖF (HULTBERG et coll 1959) to have a low energy dependence and to give good reproducibility

Sawdust was used as a substitute for air filled lungs. It had a density of 0 25 g/cm³ and was by DAHL & VIKTERLÖF (1960) found to be radiation-equivalent to an air filled lung

*Derivation of the graphical method* Expressing the dose along the beam axis in water as a function of the depth, gives as is well known straight lines in a log linear diagram for depths greater than 5 cm. This is also the case both in cork (density 0 27 g/cm³) and in sawdust (density 0 25 g/cm³) as has been shown in figures by JACOBSON & KNAUER (1956) and DAHL & VIKTERLÖF (1960) respectively Measurements have shown that at one and the same field size the quotient of the angular coefficients for the lines in sawdust and in water is approximately 2/3 This means that the percentage dose at a point within the lung is proportional to $e^{\frac{1}{3}m\,l}$ where $m$ is the angular coefficient for the line in water and $l$ is the depth in the lung

Curve 1 in Fig 1 shows schematically the dose variation with depth in the water From the said proportionality follows that the percentage dose ($P_l$) at a given point can be read from curve 1 at a depth which is $l/3$ less than the real

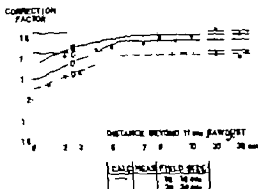



Fig. 4. Correction factor in water-equivalent material as function of the distance beyond 11 cm of sawdust (0.25 g/cm³)
Curve A constructed by the method of DUTREIX, DUTREIX & TUBIANA (1960)
Curve B constructed by the method of BURLIN (1957)
Curve C constructed by the method of MASSEY (1962)
Curve D constructed by the graphical method presented here.

tion of the distance in mix D beyond the sawdust with the field size as a parameter It will be seen in the diagram that the factor varies not only with the distance beyond the sawdust but also with the field size.

It is of course possible to establish correction factors for different field sizes and source-surface distances, and for different lung depths and distances beyond the lung, respectively but these would be very time-consuming to measure and very laborious to use in practical work. Various simplified correction methods have therefore been developed at the expense of some accuracy

BURLIN (1957) calculates correction factors for distances larger than 6 cm beyond air-filled lung by the formula

$$k_f = e^{\mu l (1-\varrho)} \tag{2}$$

were $k_f$ is the correction factor

$\mu$ is the effective absorption coefficient' in water

$l$ is the depth in air-filled lung, and

$\varrho$ is the average density of an air filled lung

For distances less than 6 cm, BURLIN introduces an additional correction to this factor At a depth beyond an air cavity the factor is multiplied by the quotient of the dose measured at this depth in a homogeneous water-equivalent material (placed at nominal source-surface distance) and the dose value at the same depth in a log linear diagram on the depth dose curve extrapolated linearly from greater depths. In the case of sawdust this additional correction factor is adopted empirically to fit the less marked increase of the factor and may be expressed as

$$k = 1 - \left\{1 - \frac{P(f\ A_0, d)}{P(f\ A_0, 6)}\ e^{-\mu(6-d)}\ \left(\frac{f+d}{f+6}\right)\right\}\ \{1-\varrho\} \tag{3}$$

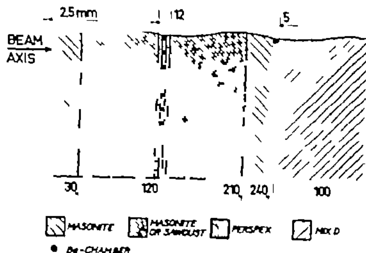



Fig 3 Cross-section through masonite phantom used to test the graphical method. The region between 30 and 210 mm can be filled with any combination of masonite sheets (30 × 30 cm) and sawdust (0.25 g/cm³) The black dots indicate Bq-chambers these are inserted into perspex sheets. Mix D is placed behind the phantom.

axis in the different cases are for the planes inside the lung cavity within ± 4 % and for the sheet at 24 cm within + 4 % to — 10 % in relation to the values calculated by the method presented here. Even for points more than half way to the edge of the beam the differences are only slightly higher For the measurement plane at 240 mm the maximum increase is + 60 % and for the planes inside the lung cavity + 40 % in relation to the uncorrected standard isodose charts

## Comparison with other methods of correction

As already mentioned several methods of correcting the standard isodose charts for air filled lungs have been described in the literature Only four methods, by which the dose distribution can be determined without making transit or exit dose measurements will be discussed here They will be compared with each other and with experimental values by an arrangement chosen with the intention of bringing the differences of the methods into strong relief To that end the methods were used to determine correction factors along the beam axis in a water-equivalent material (mix D) placed behind 11 cm sawdust A 3-cm mix D block was set up in front of the sawdust The phantom put together in this way had a cross-section of 30 × 30 cm perpendicular to the beam axis and it was placed with its front surface 80 cm from the radiation source The experimentally established correction factors for the field sizes 10 × 10 cm and 20 × 20 cm were calculated by dividing the dose values measured in this phantom by the corresponding values measured in a homogeneous mix D phantom

The correction factors determined in this way are shown in Fig 4 as a func

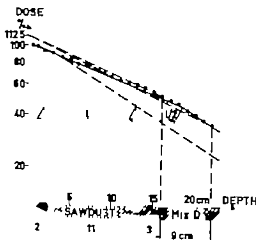



Fig. 5. Percentage dose along the beam axis as function of depth in the phantom. The phantom (cross-section 30 × 30 cm) schematically shown in the figure. The broken curves emphasized with dots were obtained by an exit dose method (Sundbom) and the solid curve by the graphical method. The dots indicate measured values; the broken curve represents the dose in water

last mentioned method. Instead, a small error is introduced because the variation of the factor with field size is not taken into account. Curve C in Fig. 4 represents this method, here standardized to the field size of 10 × 10 cm. The curves marked D in Fig. 4 were determined by using the graphical method.

On the basis of this comparison it might be concluded that the method devised by Burlin (1957) gives the best overall accuracy. On the other hand, the graphical method seems to be relatively accurate, and in manual dose planning might be preferable to the other methods because of the simplicity with which it can be applied in practice.

## Discussion

In the application of the above-mentioned methods it is necessary to know within reasonably close limits, at least the average value of the density of the lung in order to attain a satisfactory accuracy. Divergent information about the density is found in the literature. Nahon & Hawkes (1954) state that the extreme values are 0.2 and 0.78 g/cm³. In 'Clinical Dosimetry' (ICRU 1963) the range 0.25—0.4 g/cm³ is given. These values are means but the density can vary within the lung, particularly if the lung has been invaded by tumour tissue.

Chevallier & Herdly (1962) have shown that the density can vary also during the series of treatment sessions. The variation caused by respiration is generally small and is smoothed out unless the treatment times are very short. Ideally, of course, the variation in density both with time and with the position in the lung should be determined, but no method for achieving this has yet been published.

where $k$ is the additional correction factor

$f$ is the source-surface distance

$A$ is the field size

$d$ is the depth in a water-equivalent material and the distance beyond air filled lung respectively and

$P(f, A_0, d)$ is the percentage depth dose in a water-equivalent material

For a source surface distance of 80 cm a field size of 10 × 10 cm and depths greater than 6 cm $\mu$ has been calculated to be 0.050 ± 0.001 cm$^{-1}$ using depth-dose values given in Brit J Radiol Suppl 10 (1961) and following the definition of effective absorption coefficient according to JONES et coll (1956)

$$\left(\frac{f+d_2}{f}\right)^2 P(f, A_0, d_2) = \left(\frac{f+d_1}{f}\right)^2 P(f, A_0, d_1)\ e^{-(d_2-d_1)\mu} \qquad (4)$$

where $d_1$ and $d_2$ are depths greater than 6 cm.

Insertion in eq (2) of $\mu = 0.050$ cm$^{-1}$, $\varrho = 0.25$ g/cm$^3$ and $l = 11$ cm gives $k_l = 1.51$ Starting from these values and using eq (3) the curve B in Fig 4 was determined

DUTREIX DUTREIX & TUBIANA (1960) apply the same correction factors as for large distances beyond an air filled lung also near it without taking an additional correction into account They have in principle calculated the correction factor by using tissue/air ratios (JOHNS 1961) The factor can be expressed as

$$k_l = \frac{T\{A, t - l(1-\varrho)\}}{T\{A, t\}} \qquad (5)$$

where $k_l$ is the correction factor

$t$ is the total depth in the irradiated object

$A$ is the cross-section of the beam at the depth $t$

$l$ is the passed thickness of the air filled lung and

$T$ is the tissue/air ratio

For the field size 10 × 10 cm the curve A in Fig 4 was determined with the use of the values for tissue/air ratios given in the depth-dose table mentioned. At a distance of 0.3 cm beyond the lung the measured dose is 12 % lower than the value calculated in this way This is in accordance with the discrepancies of − 8 %, − 11 % and − 17 % given in this paper for lung depths of 5, 10 and 15 cm respectively (the measurements being made in perspex with a lung density of 0.4 g/cm$^3$)

Instead of applying factors valid for a large distance MASSEY (1963) used factors measured at the distance of 3 cm beyond air filled lung at a fixed field size of 8 × 8 cm (4 MV lin acc SSD 100 cm) At this field size the numerical value of the maximum error is about half that obtained by application of the

## SUMMARY

The problem of accurate dose planning in irradiation of the thorax is discussed. A short survey is given of the published methods for the solution of this problem and an additional method is described. The latter seems to give relatively high accuracy and is at the same time very easy to use in manual dose planning.

## ZUSAMMENFASSUNG

Das problem der genauen Dosisplanerung für die Strahlenbehandlung des Thorax wird diskutiert. Eine kurze Übersicht der bisher publizierten Methoden wird gegeben und eine neue Methode wird beschrieben die eine relativ grosse Genauigkeit erlaubt, und die sich bei manueller Dosisplanerung einfach zu applizieren ist.

## RÉSUMÉ

L'auteur examine le problème de l'établissement d'un plan d'irradiation précis pour l'irradiation du thorax. Il rappelle brièvement les méthodes déjà publiées pour la solution de ce problème et en décrit une nouvelle. Celle-ci paraît donner une assez grande précision et est aussi très facile à utiliser pour l'établissement manuel du plan d'irradiation.


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The average value of the density of a lung can be determined for a particular patient by measuring the transmitted dose (if the size of the lung is known). This type of measurement can be made in practice with a detector placed at a great distance from the patient and shielded against scattered radiation (JOHNS 1961) or with the aid of energy discrimination of the detected radiation (CHEVALLIER & HERDLY 1962).

There are several correction methods based on the average density measured in the direction of the treatment beam, often with the walls of the thorax included (usually expressed as water-equivalent thickness). One of these methods has been described in detail by JOHNS (1961).

It should be pointed out that if no attention is paid to the variation of the scatter within the irradiated volume, the calculated correction might be too large for points within and near the lung (cf. curve 3 in Fig. 1). The correction methods based on the absorption differences of the primary radiation alone lead to constant correction factors beyond the lung (cf. curves A and C in Fig. 3). This has been shown by BURLIN (1957).

A simple method of dose determination within the body is to draw a straight line in a log linear diagram from the measured percentage exit dose to the value 112.5 % at the surface and to read the dose from the line at the desired depth (SUNDBOM). Either the detector should be surrounded by material which gives the same amount of scatter as in standard depth-dose measurements or the detected value should be corrected for the loss of scattered radiation. When the dose at a point outside the beam axis is to be determined, the value 112.5 % should be changed into a slightly lower value. This method is illustrated in Fig. 5, in which the experimental set up is shown schematically. The total length of the phantom was about 40 cm. If the distance beyond the lung to the exit-dose detector is between 3 and 9 cm, the dose values along a line between the two broken lines emphasized with dots will be obtained. At phantom depths greater than about 6 cm the agreement with the measured doses is relatively good. The curve obtained by the graphical method is also drawn in the figure for comparison.

It is often useful to sketch the dose distribution by using the simple graphical method, whether the dose is finally determined by transit or exit dose measurements or by intracavitary measurements. The latter method has been described by DAHL & VIKTERLÖF (1960).

It should be noted in this connection that the insertion of compensating filters into the beam, as described by HALL & OLIVER (1962), makes it possible to maintain the dose distribution in accordance with the standard isodose charts at a given depth, but not in the whole of the irradiated volume when the tissue inhomogeneities are as great as in the thorax region.

DEPARTMENT OF RADIOTHERAPY HAMMERSMITH HOSPITAL, AND POSTGRADUATE MEDICAL SCHOOL OF LONDON ENGLAND

# RADIATION CANCER OF THE PHARYNX

## Case reports

by

A. W. G. GOOLDEN and R. L. MORGAN

Radiation cancer of the skin was first reported at the beginning of this century (FRIEBEN 1902). Radiation-induced tumours in the pharynx on the other hand have been recognised only comparatively recently. Most of these tumours have occurred in patients previously irradiated for thyrotoxicosis or tuberculous lymphadenitis. A characteristic feature has been the long latent interval. We report here four further cases. Two of these patients are of particular interest because of a remarkable similarity in their case histories and because the latent interval even for this type of tumour was unusually long.

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*Case 1.* A woman was given roentgen therapy for toxic goitre in 1916, at the age of 31. After she had finished treatment she developed an ulcer on the front of the neck which eventually healed. In 1957 she developed an ulcer about 1 cm in diameter on the anterior surface of the neck. The ulcer was situated just above the suprasternal notch in an area of atrophic and telangiectatic skin (Fig. 1).

Submitted for publication 5 January 1963.

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In 1956 she developed rodent ulcer on the anterior aspect of the neck. This was treated by β-ray radium pplicator

In May 1962, at the age of 75, she presented with a history of six months pain in the right ear soreness on the right side of the throat and more recently a lump t the angle of the jaw On examination she was found to have warty tumour in the right pyriform fossa. There was firm gland bout 2 × 4 cm in the middle third of the cervical chain on the right side. The skin on the anterior aspect of the neck was thin, atrophic and telangiectatic. The rodent ulcer had healed without scarring Material obtained for biopsy showed moderately differentiated squamous carcinoma.

She as treated on the linear accelerator in June 1962 receiving mean tumour dose of 6 700 rad in six weeks. Two months after completing treatment there was no visible tumour in the pyriform fossa, and the gland on the right side of the neck had resolved. When last seen, two and half years after treatment, the pyriform fossa ppeared to be clear There were no lymph nodes palpable in the neck and no other evidence of recurrence. The latent interval in this case was 45 years.

*Comments.* Both the bove patients were seen and treated in the Radiotherapy Department at Hammersmith Hospital. The other tw patients have not been seen by us. They were referred to the Radiotherapy Department in Dublin but were not given any further radiotherapy (O'Halloran 1958)

*Case 3.* A woman was given course of roentgen therapy for goitre in 1915 t the age of 40. She was given further course of treatment in 1916. She is said to have had total dose of 14 pastilles.

I 1957 at the age of 81 she presented with three months history of dysphagia and loss of eight. There was considerable amount of scarring of the skin and subcutaneous fibrosis on the right side of the neck A barium swallow showed narrowing of the cervical oesophagus and oesophagoscopy revealed complete obstruction in the lower part of the hypopharynx. Material removed for biopsy t that time did not show any evidence of malignancy but further material obtained two months later showed squamous cell carcinoma. The latent interval in this case was 42 years.

*Case 4* A woman was given course of roentgen therapy for an exophthalmic goitre in 1929 at the age of 35 Four further courses of treatment were given during the subsequent two years She is said to have had total dose of 31 pastilles. In 1957 at the age of 63 she complained of dysphagia. Oesophagoscopy revealed an obstruction in the lower part of the hypopharynx and small granulating area below the arytenoids. Material taken for biopsy showed the histologic changes of carcinoma in situ. The latent interval in this case was 28 years.

## Discussion

It is difficult to be certain about the diagnosis of radiation cancer n a particular individual because the development of a tumour in an area previously subjected to irradiation may be coincidental. There is, however fairly strong circumstantial evidence to support the diagnosis of radiation cancer in these patients.

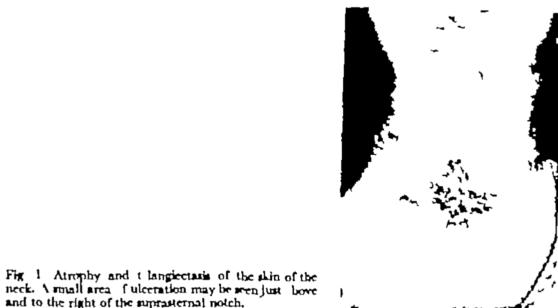


Fig 1 Atrophy and t langiectasis of the skin of the neck. A small area f ulceration may be seen just bove and to the right of the suprasternal notch.

In March 1958 the affected skin vas excised and the defect closed with a full thickness graft rotated from the chest. Histologic examination showed well-marked chronic radioder matitis in the excised skin There was a basal cell carcinoma at one edge of the specimen and in another area the epitl elium at one margin of the ulcer vas atypical and had the appearance of a squamous carcinoma.

In July 1961 at the age of 76 she presented with a history of four months dysphagia and pain in the chest She had lost one stone in weight. Oesophagoscopy revealed a tumour in the upper oesophagus extend ng as high as the crico-pharyngeus muscle Material removed for biopsy showed a moderat ly differentiated squamous carcinoma. She was treated on the linear accelerator receiving a mean tumour dose of 6 650 rad over a period of si weeks. After the treatment her swallowing improved and became almost normal. Radiologic examination shov ed some persistent smooth narrowing of the oesophagus.

In March 1964 sl e developed clinical evidence of hypothyroidism This diagnosis was confirmed by thyroid function tests and sh was started on l thyroxine 0 1 mg daily She d ed suddenly eight days after starting thyroxine

Autopsy revealed a white fibrous sca 1 cm n length almost encircl ng the oesophagus 1.5 cm below ts origin Th regional lymph nodes were not enlarged Histologic examination showed no evidence of residual tumour There were m nor irregularities of the epithel um consistent with previous radiation. Over a length of 1 cm th oesophageal muscle was com pletely replaced by dense fibrous tissue which conta ned a few cells resembling radiation fibroblasts. The thyroid vas small, weighed 10 g and appeared to be largely replaced by fibrous and fatty tissu Histologic examination showed surviving islets of thyroid tissue surrounded by ery considerable fibrosis

The latent interval in this case was 45 years.

*Case 2* A woman was treated by roentgen therapy for a toxic goitre in 1916 at the age of 29. Treatment was given once weekly for a period of on yea

In 1956 she developed rodent ulcer on the anterior aspect of the neck. This was treated by β-ray radium pplicator

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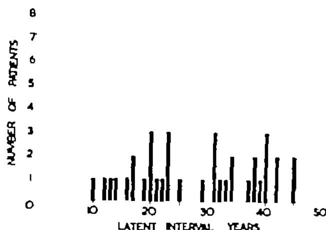



Fig 2 The latent interval in radiation cancer of the pharynx.

There have been a number of reports of tumours developing in the pharynx many years after irradiation of the neck for benign conditions We have found a total of 67 cases recorded in the literature (BABLIK 1959 BEEKMANS 1960 BOETTE 1960 CADE 1957 DEN HOED 1946 GARRETT 1959 GOOLDEN 1951 1957 HOLINGER & RABBETT 1953 KINDLER 1944 KRAHL 1960 KRUCHEN 1937 OGILVIE 1951 OMBRÉDANNE PONCET & GANDON 1954 RAVEN & LEVISON 1954 SLAUGHTER & SOUTHWICK 1957 TSUKAMOTO & TAZAKI 1954 VOSTEEN 1959 WLODYKA 1962) Examination of the records shows that the patients who developed this type of radiation cancer have many features in common Some patients were treated for tuberculous lymphadenitis but the majority were treated for thyrotoxicosis. By about 1920 roentgen rays were being widely used for the treatment of hyperthyroidism At that time the surgical treatment of thyrotoxicosis carried a high mortality rate and it is not surprising that irradiation was frequently preferred to surgery Treatment was often protracted being continued over a period of a year or more and although information about the details of treatment is usually scanty it is evident from subsequent events that radiation dosage must often have been excessive according to present day practice Patients who have developed radiation cancer of the pharynx usually have fairly severe radiation stigmata in the skin and subcutaneous tissues but in some cases the changes have been minimal It is not uncommon to find carcinoma of the skin in patients previously irradiated for thyrotoxicosis (PETERSEN 1954) Both basal and squamous cell tumours have been described Other patients have developed necrotic ulcers which have required excision and sometimes extensive plastic repair of the irradiated area Some of the patients with radiation cancer of the pharynx

have also had radiation cancer of the skin the latter condition preceding the pharyngeal cancer by a number of years. Most radiation tumours of the pharynx are situated in the hypopharynx, the post-cricoid region being by far the commonest site Several patients have developed tumours in the pyriform fossa. There appear to be only two other instances of neoplasms arising in the oesophagus (GOOLDEN 1957 SLAUGHTER & SOUTHWICK 1957) but the disease is often rather advanced at the time the diagnosis is made and it may be very difficult at that stage to decide whether it originated in the oesophagus or hypopharynx.

A characteristic feature of these tumours is the long latent interval This varies between 10 and 45 years and has a peak at about 30 years (Fig 2) It is very unlikely that such a large proportion of the patients would develop cancer after an interval of about 30 years if there were no relation between cancer and irradiation. There is, however an alternative explanation which has to be considered. It might be argued that patients irradiated for thyrotoxicosis or tuberculous lymphadenitis would most probably be in the age group 20—30 and that cancer of the pharynx commonly occurs between the ages of 50 and 60 This being so the majority of the patients might be expected to develop cancer after an interval of about 30 years Analysis of the patients with respect to age, however does not support this hypothesis. Both the age at the time of irradiation and the age at the time cancer was diagnosed vary over a wide range It may be concluded, therefore that the frequency distribution for the latent interval provides additional support for the diagnosis of radiation cancer in this group of patients.

The two patients seen in Dublin whose case histories are presented above resemble in most respects other patients who have developed radiation cancer of the pharynx. Both the patients seen at Hammersmith Hospital developed radiation cancer of the skin after an interval of about 40 years. After a further interval of four years, tumours developed in the pyriform fossa and oesophagus, respectively It is unusual to encounter cancer in either of these sites in women of this age a point in favour of the diagnosis of radiation cancer The similarity between the two Hammersmith cases is perhaps another indication of a common aetiological factor A latent interval of 45 years is longer than any so far recorded in radiation cancer of the pharynx.

It may seem irrational to treat by irradiation radiation-induced tumours but many of the patients with radiation cancer of the pharynx have in fact been treated by radiotherapy Radiotherapy is usually preferred to surgery for tumours in the laryngo-pharynx and many of the radiation-induced tumours were in any case considered to be beyond the scope of surgery Radiation changes in the skin and subcutaneous tissues have added to the difficulties

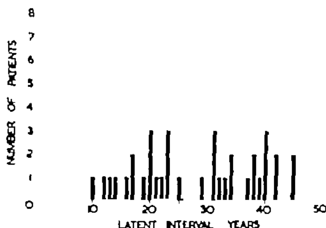



Fig 2 The latent interval in radiation cancer of the pharynx

There have been a number of reports of tumours developing in the pharynx many years after irradiation of the neck for benign conditions We have found a total of 67 cases recorded in the literature (BABLIK 1959 BEEKMANS 1960 BOETTE 1960 CADE 1957 DEN HOED 1946 GARRETT 1959 GOOLDEN 1951 1957 HOLINGER & RABBETT 1953 KINDLER 1944 KRAHL 1960 KRUCHEN 1937 OGILVIE 1951 OMBRÉDANNE PONCET & GANDON 1954 RAVEN & LEVISON 1954 SLAUGHTER & SOUTHWICK 1957 TSUKAMOTO & TAZAKI 1954 VOSTEEN 1959 WLODYKA 1962) Examination of the records shows that the patients who developed this type of radiation cancer have many features in common Some patients were treated for tuberculous lymphadenitis but the majority were treated for thyrotoxicosis By about 1920 roentgen rays were being widely used for the treatment of hyperthyroidism At that time the surgical treatment of thyrotoxicosis carried a high mortality rate and it is not surprising that irradiation was frequently preferred to surgery Treatment was often protracted being continued over a period of a year or more and although information about the details of treatment is usually scanty it is evident from subsequent events that radiation dosage must often have been excessive according to present day practice Patients who have developed radiation cancer of the pharynx usually have fairly severe radiation stigmata in the skin and subcutaneous tissues, but in some cases the changes have been minimal It is not uncommon to find carcinoma of the skin in patients previously irradiated for thyrotoxicosis (PETERSEN 1954) Both basal and squamous cell tumours have been described Other patients have developed necrotic ulcers which have required excision and sometimes extensive plastic repair of the irradiated area Some of the patients with radiation cancer of the pharynx

have also had radiation cancer of the skin, the latter condition preceding the pharyngeal cancer by a number of years. Most radiation tumours of the pharynx are situated in the hypopharynx, the post-cricoid region being by far the commonest site. Several patients have developed tumours in the pyriform fossa. There appear to be only two other instances of neoplasms arising in the oesophagus (GOOLDEN 1957 SLAUGHTER & SOUTHWICK 1957) but the disease is often rather advanced at the time the diagnosis is made and it may be very difficult at that stage to decide whether it originated in the oesophagus or hypopharynx.

A characteristic feature of these tumours is the long latent interval. This varies between 10 and 45 years and has a peak at about 30 years (Fig 2) It is very unlikely that such a large proportion of the patients would develop cancer after an interval of about 30 years if there were no relation between cancer and irradiation. There is, however an alternative explanation which has to be considered. It might be argued that patients irradiated for thyrotoxicosis or tuberculous lymphadenitis would most probably be in the age group 20—30 and that cancer of the pharynx commonly occurs between the ages of 50 and 60 This being so the majority of the patients might be expected to develop cancer after an interval of about 30 years Analysis of the patients with respect to age however does not support this hypothesis. Both the age at the time of irradiation and the age at the time cancer was diagnosed vary over a wide range It may be concluded, therefore, that the frequency distribution for the latent interval provides additional support for the diagnosis of radiation cancer in this group of patients.

The two patients seen in Dublin, whose case histories are presented above, resemble in most respects other patients who have developed radiation cancer of the pharynx. Both the patients seen at Hammersmith Hospital developed radiation cancer of the skin after an interval of about 40 years. After a further interval of four years, tumours developed in the pyriform fossa and oesophagus, respectively It is unusual to encounter cancer in either of these sites in women of this age a point in favour of the diagnosis of radiation cancer The similarity between the two Hammersmith cases is perhaps another indication of a common aetiological factor A latent interval of 45 years is longer than any so far recorded in radiation cancer of the pharynx.

It may seem irrational to treat by irradiation radiation-induced tumours but many of the patients with radiation cancer of the pharynx have in fact been treated by radiotherapy Radiotherapy is usually preferred to surgery for tumours in the laryngo-pharynx and many of the radiation-induced tumours were in any case considered to be beyond the scope of surgery Radiation changes in the skin and subcutaneous tissues have added to the difficulties

of radiotherapy but the technical advantages of supervoltage therapy may be utilised to overcome some of these difficulties

The prognosis in hypopharyngeal cancer is in general rather poor It is of some interest to note that radiation induced tumours apparently respond to irradiation at least as well as spontaneous tumours (GARRETT 1959) and the prognosis may perhaps be rather better for the patients with radiation cancer Several patients have survived for two or three years without any evidence of recurrence (GOOLDEN 1957) The results of treatment in the two patients reported here were rather better than might have been expected One is well without any evidence of disease two and a half years after treatment The other patient who died two and a half years after treatment had no evidence of residual tumour at autopsy

Information about radiation cancer in man derives mainly from cases reported in the literature These probably represent only a small proportion of the total number which have occurred The patients with radiation tumours in the pharynx now form quite a large group and it is appropriate to consider whether they contribute anything to our knowledge of radiation cancer

Comment has already been made about the latent interval which seems to be longer and more clearly defined in this type of radiation cancer than in other types Radiation cancer of the skin typically supervenes in an area of radiation dermatitis, and radiation induced tumours in bone have developed in pre-existing radiation osteitis. These observations have led to the belief that radiation tumours develop only in tissues which have suffered gross radiation damage It is not possible to estimate the radiation dose delivered to the pharynx as a result of irradiation of the neck carried out many years ago for thyrotoxicosis or tuberculous lymphadenitis but it was probably considerably less than the dose to the skin and unlikely therefore, to have produced changes in the mucous membrane of the pharynx comparable to those seen in the skin This supposition is supported by the fact that a number of these patients when submitted to further radiotherapy were able to tolerate without any ill effect a lethal tumour dose in the region of the hypopharynx It would seem then that radiation tumours may arise in tissues which have not been subjected to excessive irradiation in the usually accepted sense although tumours occurring in such circumstances may take longer to develop

Little is known about the mechanism of radiation carcinogenesis It is difficult to comprehend the process whereby ionising radiations initiate changes in the tissues which result in the appearance of a tumour after an interval of thirty years or more Prolonged or repeated irradiation has been regarded as being more likely to induce cancer than a single exposure but the effect of fractionation on tumour production has yet to be clearly defined

Little is known about the dose response relationship or the factors which determine the latent interval Some of these problems may be solved by experimental work in animals but the liability of man to develop cancer in response to irradiation can only be determined by observations in man For these reasons the collection of data on radiation cancer is of more than historical interest.

## Acknowledgements

W wish to thank Dr M. J O'Halloran for kindly supplying details of the tw patients seen in Dublin and Dr D Evans who did the post mortem examination in Case 1

## SUMMARY

Cancer of the pharynx in four female patients, who had received radiotherapy of the neck for thyrotoxicosis, is described. I tw of them, tumours in the pyriform fossa and in the oesophagus, respectively developed 45 years after the irradiation, while in the two other patients tumours in the hypopharynx developed t 28 and 42 years, respectively after the irradiation. The main features of radiation cancer of the pharynx are briefly reviewed. The latent interval for this type of tumour ranges between 10 and 45 years, with peak at bout 30 years.

## ZUSAMMENFASSUNG

Es wird uber Pharynxcancer bei 4 Frauen berichtet die wegen Thyreotoxikose eine Strahlenbehandlung des Halses erhalten hatten. Bei zwei von ihnen bildete sich 45 Jahre nach der Strahlenbehandlung ein Tumor in der Fossa pyriformis respektive im Oesophagus aus in den zwei ubrigen Fallen jedoch entwickelten sich Tumore im Hypopharynx 28 resp. 42 Jahre nach der Bestrahlung. Es wird uber die Grundzuge der Strahlenbehandlung des Pharynxcancers berichtet. Das latente Interwall erstreckt sich fur diesen Tumortyp auf 10 bis 45 Jahre mit einer Spitze bei etwa 30 Jahren.

## RÉSUMÉ

Les uteurs rapportent quatre cas de cancer du pharynx chez des femmes traités par radiothérapie cervicale pour thyrotoxicose. Chez deux d ces malades la tumeur est pparue, dans le sinus piriforme ou l'œsophage, 45 ans après l'irradiation, alors que chez les deux autres la tumeur de l'hypopharynx est apparue 28 et 42 ans près l'irradiation. Les auteurs rappellent brièvement les principaux caractères du cancer radiothérapique du pharynx. L intervalle de latence de ce type de tumeur va de 10 à 45 ans avec un maximum de fréquence autour de 30 ans.

the lesion having been constructed the exact anatomical position of the tumour is determined with due regard to a surrounding safe zone the neighbouring non affected tissue volume and the radiosensitive tissues through which the rays will pass Several methods to reach this end are in use

1 After the tumour has been demonstrated either radiographically or fluoroscopically or by both methods a number of distances are measured both on the films and the patient as well as focus to-skin and focus-to-film distances The true values must then be determined mathematically using certain proportions and taking into account the relevant correction factors (reviewed e g in ref 4 8, 16 20 21 25) Tables have been prepared that contain correction values for the diameters in film measurements (particularly for pelvimetry ref 24) The correction tables have been made for the average patient and do not take into account the individual symmetry asymmetry relationships.

2 A series of small nails are laid out (at 1 cm intervals for instance) on a piece of adhesive tape which is placed vertically on the roentgenographic couch. A double exposure roentgenogram is obtained at a known tube distance and with certain tube shifts so that a double image of each nail is produced the distance between each pair of images being related to the distance of the nail above the table The final relationships are calculated mathematically (21)

3 One or more scales, metal indicators, radiographic tape or similar objects are placed in the proper positions on the skin (6 7 11 12 14 17) The true values are then calculated

4 Roentgenography with the aid of various types of distortion-correction devices, e g similar to those used in pelvimetry (15 22) These procedures also need mathematical calculation

5 Applied orthography for plotting the anatomical details within the external contour of a particular transverse section of the body (2 3 18 19 23 34) The final values are obtained mathematically

6 Transversal tomography (e g ref 9 10 33) which however is not possible if the patient is recumbent Such a roentgenogram must be corrected for magnification before it is projected into the corresponding cross-section

7 Different types of calipers particularly for accessible lesions (such as those of the cervix) as well as for pelvic measurements and for the estimation of the true diameters of the pelvic brim (e g ref 1 15 22 30 31) These also need mathematical calculations corrected by a number of factors.

Whatever the technique chosen to localize the tumor in the interior of the body it is now the universal practice to check the accuracy of the field localisation during the prolonged series of treatments by roentgenograms obtained

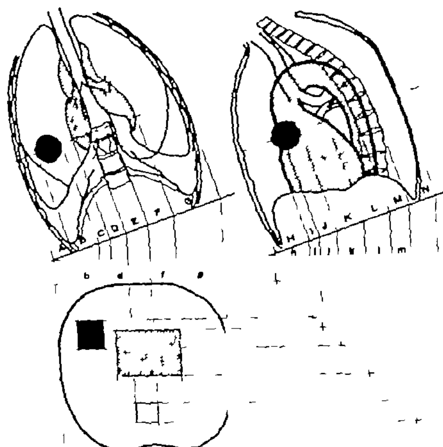



Fig. 1 Sketch illustrating two roentgenograms obtained at right angles, and transversal body-contour equivalent made at the level indicated. The fundamental principle of placing the image of the lesion (black spheres), heart and spine to the cross-section is apparent.

with the therapy beam through the fields selected (18 19) The procedure gives, however no direct information on the accurate assessment of the position and size of the neighbouring non-affected, more or less *radiosensitive tissues.*

## New technique — main features

Several modifications of the device described below have been made. The underlying idea of the present technique for positioning roentgenologic images onto the corresponding ready *body-contour equivalents* (prepared by the technique in ref. 27) appears in Fig 1 which is a simplified sketch.

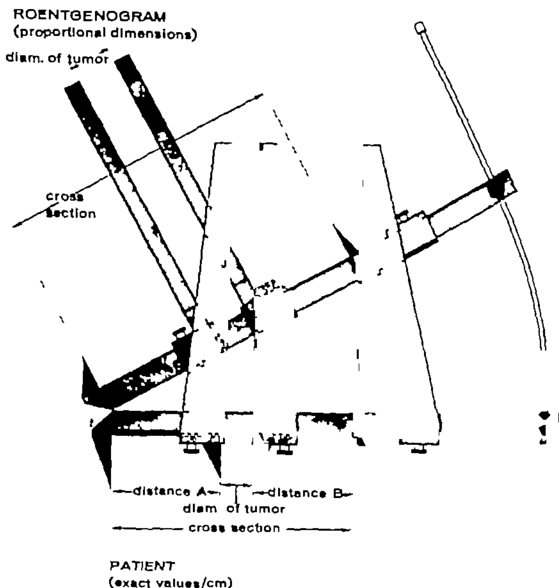



Fig 2. Schematic representation of the device.

The initial step in the procedure consists of a roentgenologic examination in which the patient is fluoroscoped and roentgenographed in exactly the same position(s) in which he will later be placed during the irradiations Fluoroscopy gives information about the general location and spread of the lesion i e whether it is in the dorsal medial or ventral, and right median or left parts of the body This information determines the technique of producing the roentgenograms in either an antero-posterior or postero-anterior direction and the selection of exposures between both the lateral protections. The surface

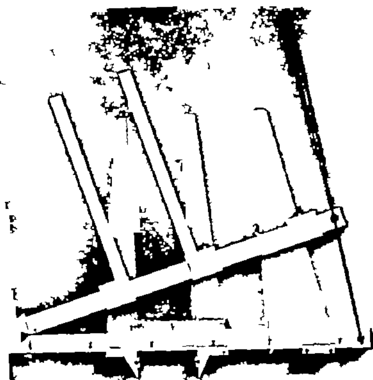


Fig. 3. One of the prototypes. The true value (in cm and mm) of the image is directly readable between the two perpendicular arms in the middle of the lower leg

contours of the patient are indicated with suitable landmarks, preferably by radiographic tape or tattooing. The landmarks serve, on the one hand to determine exactly the external soft tissue boundaries (skin) on the other hand they will later be used for the proper positioning of the patient during the irradiation and follow up stages. The roentgenograms are obtained (1) from two angles, with the respective central ray(s) passing through and intersecting at the center of the lesion, and (2) without changing the position of the patient between the exposures.

A rounded lesion (black spheres) is drawn in the middle lobe of the right lung in Fig. 1. The transfer of this image to the cross-section is done by taking advantage of the mathematical principle according to which a line of known length (here the diameter in the true cross-section) is geometrically subdivided or fractioned into parts so that the lengths of the resultant parts equal the distances desired in the roentgenogram (here, diameters in the film). A new




Fig 4 The device in clinical use a) Th placing of the roentgenologic (proportional) distances onto the upper leg b) Tl e resultant accurate d true value is transferred to body-contour equivalent.

device (Figs 2 and 3) is used to carry out this procedure without any mathematical calculation (26) and consists of two legs connected by a joint to form an adjustable angle and a number of manually transferable arms lying at right angles against the respective legs. The distances desired from the roentgen films are placed in unbroken succession (A—G in Fig 1 left and H—N in Fig 1 right) on the upper leg and one diameter (a—g and h—n) only upon the lower leg the arms of which are adjusted to intersect those of the upper leg (Figs 2 and 3) The proportional distances in the roentgenogram thus become directly converted to exact values (cm and mm) and may be placed onto the cross-section (Fig 1) The procedure of measuring and placing one complete image on the body-contour equivalent takes, on an average a minute

Fig 4 shows the device in use Pencils have been inserted into the touching tips in one of the prototypes and facilitates the procedure (Fig 4b)

The device is rapid and accurate in use and automatically gives the true relevant values directly without any calculation As the idea is based on a purely geometric principle the performance is not subject to errors in calculation

Various clinical applications of this device and of the one previously described (in ref 26 27) will be published separately in papers to follow (28 29) Clinical studies have revealed surprising asymmetry in the human body and

a significant variation in the topographic location of the organs. This applies both to clinical subjects and apparently normal controls. One of the most important findings was that the position of the patient, and even infinitesimal changes in it, alter the topography and size, even of so-called fixed organs and structures, in a highly significant manner

## SUMMARY

A simple and accurate technique employing special device for dose planning in radiotherapy is described.

## ZUSAMMENFASSUNG

Es wird über eine einfache und akkurate Technik mit einem Gerät zur Dosisplanierung bei Strahlentherapie berichtet.

## RÉSUMÉ

Description d'une technique simple et précise utilisant un dispositif spécial pour déterminer les doses nécessaires en radiothérapie.

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# SYSTEMATIC ARC CALIBRATION METHOD FOR BODY RADIOACTIVITY MEASUREMENT

by

A. L. LILLEGRAVEN and J RUNDO

The establishment of absolute correspondence between body activity content and instrument response is a major problem in whole body counting techniques (MARINELLI et coll 1955 MILLER & MARINELLI 1956, RUNDO 1958 1962) The most rigorous calibration method consists in injecting a known amount of the nuclide into the subject, or into another person of similar build, and measuring the response at an appropriate point in time. However this may at worst be inadmissible and is at best not very convenient. Other less rigorous methods must therefore often be employed.

*Arc calibration methods* The so-called arc method, in which the subject is placed in such a position that the body is bent along an arc of a certain radius, is commonly employed. The detector is placed at the centre of the defining circle Its response to radiation from different parts of the body is largely equalized, and the body activity may be simulated to a good approximation by a point source embedded in a phantom this must have a form and consistency to simulate absorption and scattering by the average or a more specific body section.

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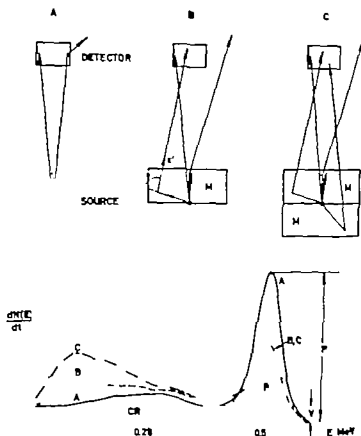



Fig 1 Effects on the gamma-ray spectrum due to absorption and scattering in phantom material (E = 0.51 MeV in example)

The uniformity of response in depth increases with radius, and this applies also to the comfort of the person being measured The counting efficiency on the other hand decreases sharply with increasing radius. A compromise must be decided upon and in practical cases the radius may be between 1 and 2 m (EVANS 1937 MARINELLI et coll 1955 MILLER 1962)

*Phantom considerations* The choice of a phantom involves selection of a matrix material as well as shape for the building blocks. After these decisions have been made, it remains to determine the overall dimensions and the position of the point source within the phantom

If the measuring equipment does not permit gamma ray energy analysis, and no knowledge of the nuclide distribution is at hand average conditions must be assumed i e the matrix thickness is set equal to the average body thickness and the point source is placed at the centre Normally the dis-

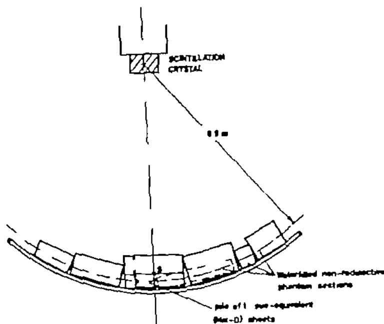



Fig 2 Arrangement of phantom on the re. S — source, — number of sheets (= cm) bov S, b — number of sheets below S

tribution in the body will be known to some extent and this knowledge is taken into account.

When a gamma-ray spectrometer is available, however spectrum modifications due to the phantom will provide additional information which may be used to determine phantom dimensions and source positioning.

*Effects of the phantom on spectral shapes* The spectral modifications taking place when absorbing and scattering material is introduced in the source surroundings are illustrated in Fig 1 Spectrum A, obtained when essentially no absorption and scattering takes place outside the scintillation crystal, is regarded as the basic spectrum. The photopeak $P$ corresponds to incident photons totally absorbed in the crystal, while the Compton region $CR$ is produced by single or multiply-scattered photons leaving the crystal volume within wide energy limits.

The spectral changes introduced by adding material $M$ in front of the sou ce (see $B$ Fig 1) are mainly due to (1) absorption (including scattering out of beam) and degradation, and (2) forward scattering into the beam.

Referred to the basic spectrum the main changes caused by (1) and (2) are respectively, (I) proportionate reduction of whole spectrum and an increase at low energies (~0.1 MeV) and (II) a relative increase in the number of counts in the Compton region especially at energies a little below the primary quantum energy.

For $M$ thicknesses of practical interest the net effect of (I) and (II) is an increased counting rate in the Compton region and a decreased counting rate in the photopeak. The modified spectrum is shown in the figure (curve B).

The only effect of adding further material $M_b$ behind the source spectrum C is relative to spectrum B an enhanced counting rate in the low energy region. Curve C in Fig. 1 indicates the modification due to $M_b$.

*Criteria for stipulating best simulation.* A method introduced by MILLER & MARINELLI (1956) in which the spectrum from the subject is matched with that obtained from a point source buried in a Presdwood phantom, will now be considered. Material is added in front of and behind the source until the phantom spectrum is similar to that of the subject. The radioactive content of the subject is finally determined by simple proportion. The criteria for spectrum matching are not stated quantitatively.

The ultimate criterion for full similarity would be complete matching channel by channel over the entire spectrum. Such a criterion can only be fulfilled if we assume a spectral continuum and no statistical fluctuations. Even allowing for statistics and the finite number of channels, matching would often not be feasible without having recourse to distributed sources in elaborately shaped phantoms. Simpler but carefully chosen criteria must be employed in practice.

The peak-to-valley ratio ($p/v$ Fig. 1) has been proposed as giving a sensitive measure of the amount of material covering the source, e.g. to differentiate between surface and internal contamination (RUNDO 1958). While this effect may be used in many cases, doubts may be raised as to the value of this quantity in cases of low body radioactivity as it is also very susceptible to statistical fluctuations.

A systematic method with simplified criteria for matching body and phantom spectra will now be described.

## Systematic calibration method

The phantom is built up as illustrated in Fig. 2. One section of the phantom is a pile of tissue-equivalent sheets (mix D) each 29.5 × 29.5 × 1 cm with a point source placed centrally in one of them. The numbers of sheets (or

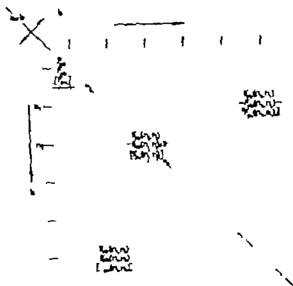


Fig. 3. Tables of spectrum indices (see text for explanation)

centimetres of material) above and below the source are denoted $a$ and $b$ respectively

Calibration spectra are recorded systematically for all combinations $(a, b)$ within reasonable ranges of $a$ and $b$ and the following quantities are extracted from each spectrum

the total counting rate $R_p(a, b)$ in the photopeak

the ratio $F_Q(a,b) = R_c(a,b)/R_p(a,b)$ where $R_c(a,b)$ is the total counting rate in the Compton region

the peak-to-valley ratio $F_{pv}(a, b)$ and finally for all combinations $(a = n_i, b = n_k)$ and the 'symmetrical' combinations $(a = n_k, b = n_i)$ values are calculated of the ratio,

$$F_{ab}(n_i, n_k) = \frac{R_p(n_i, n_k)}{R_p(n_k, n_i)}$$

Obviously

$$F_{ab}(n_i, n_k) = \frac{1}{F_{ab}(n_k, n_i)}$$ and $F_{ab}(n_i, n_i) = 1$ by definition

These quantities are next recorded in tabular form, as indicated in Fig 3

Now by interpolation along horizontal ($b$ = const) and/or vertical ($a$ =

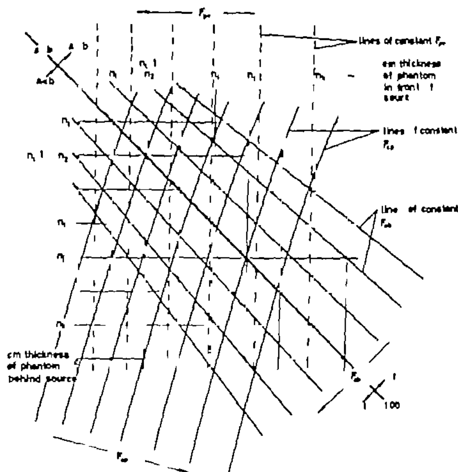



Fig 4 Calibration chart derived from fig 3

const) lines these tabulated values may be converted into a more useful calibration chart The latter shown in Fig 4 displays lines of constant $F_{\gamma p}$ $\Gamma_{ab}$ (and $F_{pe}$)

*Use of calibration chart* The subject whose body radioactivity content is to be determined is measured twice in the arc arrangement once on the back and once on the front The quantities ${}^fF_{\gamma p}$ ${}^b\Gamma_{\gamma p}$ ${}^fF_{ab}$ ($= {}^fR_p/{}^bR_p$) and ${}^bF_{ab} = {}^f\Gamma_{ab}^{-1}$ (if desired also ${}^fF_{pe}$ and ${}^bF_{pe}$) (where the superscripts $f$ and $b$ denote on front and on back ) are determined

The point-source/phantom simulation method implies as do all related calibration methods that full matching of body and phantom spectra is tantamount to equivalence between total body and point source activities Furthermore as linearity between detector response and the activity in any

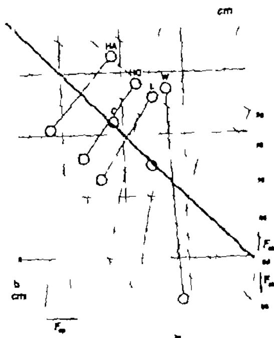



Fig. 5. Calibration points for five subjects containing strontium 85.

fixed geometry may normally be taken for granted, simple proportion applies in the general case of spectral similarity alone i. e.

$$s = \frac{r}{R(a,b)} S \tag{1}$$

where $s$ and $S$ are subject and point-source activities, and r and $R(a,b)$ integral counting rates over any region common to the subject and phantom spectra, respectively. (Total counting rate or photopeak counting rate are practical choices.)

If we now plot the point ($^{f}F_{ab}/F_{ap}$) on the calibration chart, the corresponding phantom combination ($a_1,b$) — $a$ and $b$ will generally not be integers, and $R(\ ,b)$ is found by interpolation — may be read directly and the body content $s$ may be determined from eq. (1). Also point ($^{b}F_{ab}$, $F_{ap}$) selects a combination ($a_2$, $b_2$) on the chart and a value $s''$ for the body content. Ideally $F_{ab}$, $F_{ap}$) must be positioned symmetrically to ($^{f}F_{ab}$ $^{f}F_{ap}$) with respect to the diagonal corresponding to $a = b$. Turning of the subject corresponds to turning of the phantom, consequently ($a_2$, $b_2$) = ($b_1$ $a_1$) symmetrical to ( $b$ ). It necessarily follows from this that $s$ is equal to $s$

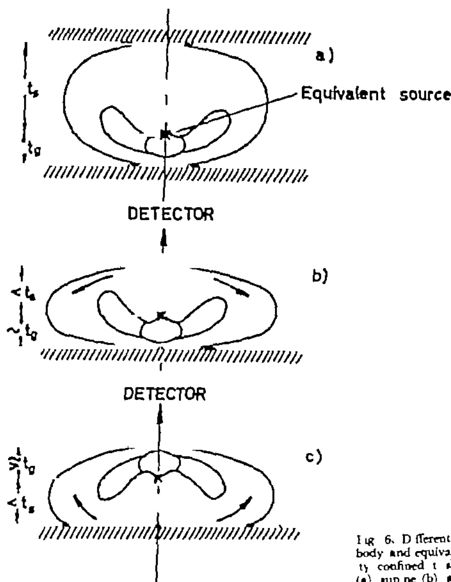



Fig. 6. Different configurations of body and equivalent source (activity confined to skeleton) standing (a), supine (b) and prone (c)

*Experimental.* The 85Sr contents of five human subjects had to be determined in the course of strontium retention studies (RUNDO et coll. 1964) carried out in collaboration with G. E. Harrison of the Medical Research Council's Radiobiological Research Unit, Harwell, England. The measurements took place some days after the cessation of the intake period and it could therefore be assumed that nearly all the strontium (a bone seeking nuclide) was deposited in the skeleton.

From the net 85Sr spectra indices $^{f}F_{ab}$, $^{b}F_{ab}$ $(= {}^{f}F_{ab}^{-1})$, $^{f}F_{ac}$ and $^{b}F_{ac}$ were extracted and plotted on a Sr

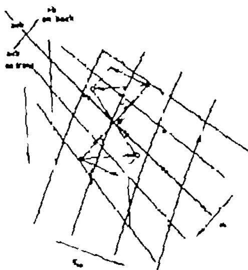



Fig 7 Effects of body elasticity Solid circles are symmetrical calibration points, in the ideal case of the rigid body open circles re calibration points for the elastic body

calibration chart, according to the method described above (Fig 5) Conjugate points are interconnected.

*Deviation from symmetry* It appears from Fig 5 that the symmetry rule applies well for three of the point pairs, viz *HA*, *HO* and *L*, whereas cases *C* and *H* differ markedly No attempts will be made to discuss in full the reasons for the discrepancy These have to do with the range of validity of the simulation method itself the assessment of which is difficult. However attention is drawn to an effect which is easily deduced qualitatively and which may account very largely for the observed differences.

The calibration method requires turning of the body from the prone to the supine position. Obviously it also demands that all body sections are rigid during this process, i e no sagging within the body is allowed by analogy with the phantom. In practice the elasticity of the human body must be accepted as a fact and an attempt will be made to evaluate its effect on the calibration

The activity is deposited in the skeleton in the particular examples discussed and it will be assumed that the spine and the hip-bones are the parts of the skeleton most affected by lack of rigidity Average body cross-sections are outlined in Fig 6, in an exaggerated manner for three different postures the erect body is illustrated in (a) and in the others the body lying on the arc stretcher

in supine (b) and prone (c) positions, respectively. It may be assumed in relation to the spectrum for the rigid body that the spectra from the non-rigid body should deviate as illustrated below.

| Body position | Effect on the body | Effect on the gamma spectrum | Effect on the calibration indices |
|---|---|---|---|
| Supine | Source-detector distance little affected, less absorbing material between activity and detector | Photopeak larger, probably the same or lower Compton region | Decrease of $F_{cp} = \frac{R_c}{R_p}$ |
| Prone | Source-detector distance larger, forward scattering volume increased, back-scattering volume decreased | Photopeak smaller, Compton region probably the same or higher | Increase of $F_{cp} = \frac{R_c}{R_p}$ |
| Combined, assuming ${}^fF_{ab} > {}^bF_{ab}$ for a bone-seeking nuclide | | | ${}^fF_{ab}$ will decrease and ${}^bF_{ab}$ increase |

The resulting deviations are depicted graphically in Fig. 7.

If we now compare the derived deviation with that observed for cases *C* and *W*, it is evident that both go in the same direction. Cases *HA*, *HO* and *L* also display the same tendency, but little reliance can be placed on this as the deviations are of the same order of magnitude as the statistical fluctuations. — It should be noted that in all cases ${}^fR_p > {}^bR_p$, or ${}^fF_{ab} > 1$, i.e. more of the body activity is positioned near the back. This is contrary to observations made by MILLER & MARINELLI (1956) on the distribution of $^{226}$Ra, another bone-seeker, but in agreement with their findings with $^{90}$Sr.

Pursuing this line of reasoning, one will expect the magnitude of the deviation to be a function of body elasticity. More specifically, less rigidity will lead to larger deviations. Such a tendency may be deduced from Fig. 5 if we accept a relationship between body softness and body thickness.

One way of obtaining a relative measure for the average body thickness is to calculate the ratio $W/H$, where $W$ and $H$ are body weight and height respectively.

Another measure of body thickness is inherent in the diagram of Fig. 5. A phantom combination $(a, b)$ with a total thickness $a + b$ corresponds to each calibration point. Average thickness deduced from two conjugate points, $((a + b)_f + (a + b)_b)/2$, is very nearly equal to that derived from the intersection point between the interconnecting line and the diagonal $a = b$; the latter is chosen for the sake of convenience. The existence of a positive correlation between $W/H$ and $(a + b)$ is apparent from Fig. 8, and it is noteworthy that the straight line drawn between the points passes through the origin. This indicates that $W/H$ may be a sensible measure of body thickness.

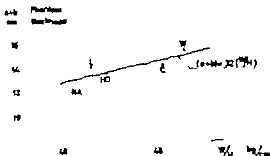


Fig 8. Correlation between two different measures of body thickness.

in this case, although, because both the distance of the points from the origin and the scatter about the line are considerable, it is not definite. ($\sqrt{W/H}$ would be a more correct measure presuming exact axial proportionality between bodies of all sizes. However proportionality is certainly not a firm rule and with large values of $W/H$ the trunk is liable to be mainly responsible.)

Returning to the considerable deviation from symmetry in cases $C$ and $H$ it is evident from Fig 8 that they also form a separate group with respect to body thickness as measured by $W/H$. This strongly suggests that body elasticity is the principal phenomenon responsible for non-symmetry

*Determination of the body activity* This is described under subheading Use of calibration chart for cases where the two calibration points are symmetrical to each other In all other cases $s$ and $s$ will differ and the body content is then set equal to $s_m = \frac{s' + s}{2}$. If $F_{ab}$ is not too different from unity however another and more convenient procedure may be used

Both calibration points are displaced by an equal amount in Fig. 7 as this seems reasonable when no quantitative knowledge on the displacement mechanism is at hand. However one point remains fixed during the displacement, viz. the point of intersection 0 between the diagonal ($a = b$) and the interconnecting line It can be shown with reasonable assumptions, that the body content is given approximately by the expression

$$= \frac{\frac{1}{2}({}^{f}r_p + {}^{b}r_p)}{R_p(\pi_p, \pi)} S \qquad (2)$$

where and ${}^{b}r_p$ are body photopeak counting rates on the front and on the back respectively $R_p(\pi_p, \pi)$ is the phantom photopeak counting rate corresponding to the pivot point 0, and $S$ is the activity of the point source.

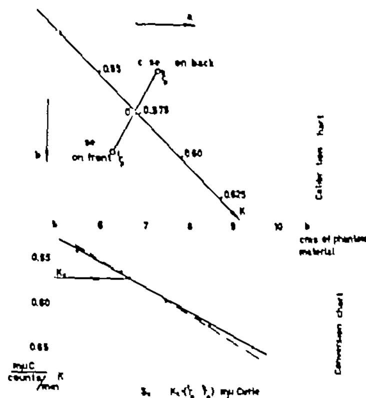



Fig 9 Simplified determination of radioactive content of body The measurement points ( ) determine the calibration line (continuous) The broken line shows the theoretical slope

Eq (2) invites an extension of the calibration chart making the activity determination very simple If eq (2) is arranged as follows

$$s \quad ({}^{f}r_{p}+{}^{b}r_{p})\,\frac{S}{2\,K_{p}\,(n, \; n)} \quad ({}^{f}r_{p} + {}^{b}r_{p})\,K$$

it becomes evident that the diagonal may be calibrated directly in terms of $K \dfrac{\mu\mathrm{Ci}}{\mathrm{counts/min}}$ A conversion chart may also be put beneath the calibration chart Both alternatives are shown in Fig 9 The conversion line illustrated in this diagram is that obtained from the actual Sr calibration measurements

A theoretical calibration line has also been drawn this is derived from

$$K \quad C\,(90 \;-\, n_{i}) \;\; \exp(\sigma n_{i})$$

where $n_i$ is the half thickness of the phantom and $\sigma$ is the linear absorption coefficient of the phantom material $C$ is a factor which is a function of the size of the crystal and of the gamma ray energy The line drawn in Fig 9 was forced through the centre of gravity of the measured points by adjusting the value of $C$ The difference between the theoretical and measured slopes

may be largely due to an increased contribution to the measured photopeak counting rates from forward scattered gamma rays, as the relative contribution increases with increasing phantom thickness (see Fig 1 curves A and B)

## Discussion

Calibration of whole body counting arrangements by phantom/body spectral matching appears to be a well established method Normally the body spectrum is measured first, followed by a trial-and-error procedure, in which the phantom is rearranged until its spectrum matches that of the body The criteria for matching may differ and are not always firmly defined.

The procedure described in this paper differs in two respects

A. Phantom spectra are first recorded systematically and are used for preparing a calibration chart. This chart is used for all subsequent body activity measurements on the same nuclide, provided no drastically different geometry or distribution is encountered

B. The use of the quantities $F_{\phi}$ and $F_{\Delta}$ as spectrum indices for assessing spectral matching.

Doubts may be raised as to the practicality of preparing a calibration chart if only a few cases are to be measured. We have however found that the time required is not too long when a reasonably strong source is employed, and the use of a modern multi-channel pulse amplitude analyser with sophisticated read-out equipment facilitates the accumulation of the necessary data.

No claim is made for the ultimate advantages of $F_{\phi}$ and $F_{\Delta}$ as spectrum descriptors. They reflect features of the spectrum that seem to be reasonably susceptible to differences in distribution of the activity and in body shapes. At the same time they can be determined with fairly high precision even when the statistical fluctuations on individual channel counting rates are considerable The lines of constant $F_{\phi}$ cross those of constant $F_{\Delta}$ at angles approaching 90° as may be seen from Fig 5 and this is of considerable help as regards resolution of the calibration points. Nevertheless better indices may certainly be found by consideration of the discussion on the effects of the phantom on spectral shapes.

Inevitably there must be a limit as to how much information may be extracted. Improvements will change from real to superficial ones when the possibilities of the single point source phantom are exhausted. The arc method is however valuable because of its simplicity and further investigations into its range of validity should be welcomed.

## Addendum in proofs

Since this paper was submitted for publication we have obtained some evidence of the accuracy of the method. An intravenous injection of 2.25 μCi of barium 133 was administered to a volunteer subject, body radioactivity measurements were made using a crystal 9 inches in diameter by 6 inches thick and an arc radius of 170 cm, and a calibration chart was prepared as described in the text. The results obtained are compared with those from measurements of the cumulative excretion in the following table. During the 13 days follow-

| Days after injection | (A) Body content μCi | (B) Cumulative excretion μCi | $\frac{A}{2.25-B}$ |
|---|---|---|---|
| 0 | 2.10 | 0 | $0.93_5$ |
| 1 | 1.49 | 0.65 | 0.93 |
| 2 | 0.86 | 1.29 | 0.90 |
| 3 | 0.58 | 1.64 | 0.95 |
| 4 | 0.47 | 1.71 | 0.87 |
| 6 | 0.34 | 1.88 | 0.92 |
| 8 | 0.29 | 1.94 | 0.93 |
| 10 | 0.25 | 1.98 | $0.92_5$ |
| 13 | $0.22_4$ | 2.01 | 0.94 |

ing injection the value of $K$ varied unsystematically between 0.42 and 0.47 $\frac{\mu Ci}{\text{counts/min}}$; there appears to be a systematic error in estimating the body content but this only exceeded 8 per cent on two occasions. When the results are converted to percentage retention i.e. 100A/2.10 and 100-100B/2.25 the agreement is excellent.

## Acknowledgements

This work was carried out while one of us (A. L.L.) was on leave of absence from the Norwegian Defence Research Establishment, Kjeller, Norway, financed by N.D.R.E. and by a research fellowship from the Royal Norwegian Council for Scientific and Industrial Research. We wish to thank Miss J. I. Mason for the help with measurements of gamma ray spectra from the phantom. Mr P. D. Cross made the measurements of gamma ray spectra from the phantom and prepared the calibration chart mentioned in the addendum.

## SUMMARY

In the arc technique for calibrating whole body counting arrangements, the radiation emitted by the body is simulated by that from a point source in a phantom. A procedure is described in which phantom spectrum information is extracted systematically and then used for preparing a calibration chart which can be employed in all subsequent body activity measurements of the same nuclide. Its application is illustrated by the results of measurements on five human subjects after their intake of strontium 85.

## ZUSAMMENFASSUNG

Es wird eine Methode beschrieben, die es erlaubt systematisch Phantomspectrumdaten zu erhalten, und mit der es dann moglich ist eine Kalibrierungstabelle fur spatere Aktivitätsmessungen desselben Nuklides aufzustellen. Die Anwendungsmöglichkeit der Methode wird demonstriert, mit Resultaten von Messungen an 5 Personen die Strontium 85 in ihren Geweben enthielten.

## RÉSUMÉ

Dans la technique de l arc pour l'étalonnage de dispositifs de comptage de tout le corps, le rayonnement émis par le corps est simulé par celui d'une source ponctuelle située dans un fantôme. L auteur décrit comment l'information concernant le spectre du fantôme est extraite systématiquement et utilisée pour préparer une fiche d étalonnage qui peut servir pour toutes les mesures ultérieures d'activité corporelle du même nuclide. Son application est illustrée par les résultats de mesures sur cinq sujets humains après administration de strontium 85.

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# INTEGRAL ABSORBED DOSES IN ROENTGEN DIAGNOSTIC PROCEDURES

## II — Measurement of integral doses in two roentgen diagnostic departments

by

CARL CARLSSON

The medical use of ionizing radiation is responsible for the major part of the exposure of people to man made radiation sources particularly in advanced countries Table 1 compares the annual dose equivalent from natural radiation sources to the annual genetically significant dose together with gonad and mean doses from roentgendiagnostic examinations. Though roentgendiagnostic examinations as a rule give small doses to the individual these radiation doses may as they are given to many persons, be of interest in attempts to determine possible relations between radiation doses and biological effects.

For large radiation doses some relationships between dose and biological effects are relatively well understood From these results it is difficult to make conclusions regarding the effects of small doses Measurements of the small radiation doses delivered in roentgendiagnostic examinations may be of value for epidemiological examinations to determine a possible relationship between small radiation doses and the frequency of malignant diseases (UNESCO, ICRP and ICRU) If any relationships of this kind are proved in another way

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Table 1

*Radiation doses in Sweden for adults*

| Radiation source | Dose equivalent, mrem: Gonads | Dose equivalent, mrem: Average in total body |
|---|---|---|
| | Annual dose equivalent | |
| Natural radiation sources (UNSCEAR) | 100—230 | 150—300 |
| *Roentgendiagnostic examinations.* | | |
| I. Genetically significant dose equivalent (Larsson) | 28—48 | — |
| II. Individual doses | Dose equivalent per examination | |
| Colon | 40—2900a | 200—3300b |
| Stomach | 2—160a | 120—2500b |
| Urography | 20—2600a | 90—1900b |
| Cholecystography | 1—40a | 10—700b |
| Chest | 1—10a | 20—250b |

a) Larsson, b) Tables 3 and 4.

measurements may be valuable for analysing the possible risks of irradiation from roentgendiagnostic examinations.

Radiation doses to small organs, for example, the gonads and eyes, may sometimes be measured directly on the patient with point-shaped detectors. If the whole body or a diffuse organ, as active bone marrow are irradiated, a point measurement is of little value if the dose varies markedly within the organ or body. In these cases the integral dose in the organ or in the whole body is of greater value. The integral dose in active bone marrow that is of interest in studies of the frequency of leukaemia is, however, difficult to estimate owing to both dosimetric difficulties and our lack of knowledge concerning the amount and distribution of the active bone marrow (UNSCEAR). The integral dose in the whole body hereafter called simply integral dose, may as has been discussed in the preceeding part of this article, be measured in routine roentgendiagnostic examinations. The value of integral dose data may appear doubtful, but if information about the part of the body being irradiated is included, these data ought to be useful *in epidemiological studies.*

## Present work

Results from measurements of integral doses from routine roentgendiagnostic examinations are reported and analysed. The measurements were performed from 1958 to 1961 in the roentgendiagnostic departments of one university hospital (Lund) and to a smaller extent in one community hospital

**Table 2**

*Roentgen units used in the integral dose measurements*

| Examination room | Roentgen tube | Maximum voltage, kV | Grid ratio | Total filtration with monitor mm Al | Voltage pulses per period: Roentgenograms | Voltage pulses per period: Fluoroscopy |
|---|---|---|---|---|---|---|
| Lund 1 | Overcouch | 200 | 1 16 | 3 5 | 12 | — |
| | Undercouch | 120 200 | 1 6.5 | 4 0 | 12 | 2 |
| | Forssell stand | 200 | 1 6.5 | 4 0 | 12 | 2 |
| | Horizontal beam | 90 | 1 6.5 | 1.2 3.5 | 12 | 2 |
| Lund 2 | Overcouch | 120 | 1 6.5 | 3 6 | 2 | — |
| | Tomograph | 100 | 1 6.5 | 3 1 | 2 | 2 |
| Lund 3 | Overcouch | 100 | 1 6.5 | 2 8 | 6 | — |
| | Undercouch | 100 | 1 6.5 | 3.3 | 6 | 2 |
| | Forssell stand | 100 | 1 : 6.5 | 3 1 | 6 | 2 |
| Lund 4 | Overcouch | 90 | 1 6.5 | 3.6 | 6 | — (Condenser) |
| Lund 5 | Universal stand | 125 | 1 6.5 | 2 9 | 6 | 2 |
| Lund 6 | Overcouch | 80 | 1 6.5 | 6 | 6 | — |
| | Undercouch | 100 | 1 6 5 | 3.8 | 6 | 2 |
| | Forssell stand | 100 | 1 6.5 | 4.3 | 6 | 2 (Condenser) |
| Lund 7 | Universal stand | 125 | 1 6 5 | 3 9 | 6 | 2 |
| Lund 8 | Overcouch | 110 | 1 6.5 | 2 4 | 6 | — |
| | Undercouch | 110 | 1 6.5 | 2 7 | 6 | 2 |
| | Forssell stand | 110 | 1 6.5 | 3 0 | 6 | 2 |
| | Filmchanger | 110 | 2×1 6 5 | 3 6 | 6 | — |
| Halsingborg 2 | Overcouch | 100 | 1 6.5 | 3 4 | 6 | — |
| | Undercouch | 100 | 1 6.5 | 2 8 | 6 | 2 |
| | Forssell stand | 100 | 1 6.5 | 1 8 | 6 | |
| Halsingborg 3 | Overcouch | 100 | 1 8.5 | 3 4 | 6 | — |

(Hälsingborg) In all, about 2 000 measurements of integral dose have been recorded The monitors have been mounted on 23 roentgen tubes in 10 examination rooms. Twenty five roentgenologists mainly physicians in training have performed the roentgen examinations

The results of the integral dose measurements and the distribution of integral

dose between fluoroscopy and roentgenograms are shown in tables for the different roentgen examinations. In addition the tables also give (1) mean dose (the average value of the absorbed dose in the whole body — that is, the integral dose divided by the body weight) and (2) the primarily measured quantity $\int_A X dA$ (the areal exposure) measured in units of R cm

The mean dose may be directly compared with the dose-equivalent from uncollimated radiation sources, for example external and internal irradiation from naturally occurring sources and fallout from nuclear weapons (see Table 1)

## Technical equipment in the departments

*Roentgen units* Table 2 gives data for all of the roentgen units with which integral dose measurements have been made. In one case in Table 2 two different values are given for the maximum voltage (undercouch Ld 1) (Lund is abbreviated to Ld Hälsingborg to Hbg) The lower value of 120 kV is valid before 1961 the higher value in 1961

Two roentgen tubes lacked filters. In one case (horizontal beam Ld 1) a filter was added during the measurements. Two values of the total filtration of this tube are therefore given in Table 2 (see also Fig 5) During a certain period of the measurements, an experimental model of an automatic exposure timer was used. The timer was mounted between the secondary radiation grid and the film or screen. Owing to this location the timer reduced the exposure to the film and screen by 10 to 30 % causing increased irradiation to the patients. The timer could not be used with roentgenograms smaller than 13 × 13 cm a disadvantage causing higher integral doses. The appropriate exposure time chosen by the experimental timer usually caused a reduced number of unsatisfactory roentgenograms, a fact counteracted by occasional malfunctions, sometimes also by improper use.

At the university department in Lund the films were developed automatically therefore the exposure data (kV and mAs) had to be chosen more carefully than in Hälsingborg where the films were developed manually and individually A further technical difference between the two departments was the way in which the exposure data were matched to the thickness of the patient. In Lund only the exposure time was adjusted (the mAs value) — in Hälsingborg also the voltage was varied.

*Types of films and screens* Standard film was used during the main part of the measurements in Lund. A change to rapid film, primarily motivated by a high contribution to the integral dose from the roentgenograms, led to repeated

**Table 5**

*Results of measurements of integral doses in examinations of colon, stomach, gallbladder and lungs.*

| Examination | Exam. room | Integral dose kg rad | | | |
|---|---|---|---|---|---|
| | | Max. | Min | Median | Mean |
| Colon barium enema | Ld-6 | 160 | 19 | 53 | 57 |
| | Ld 1-aut | 400 | 22 | 59 | 68 |
| | Ld 1 | 120 | 22 | 51 | 61 |
| | Ld 1 rap | 76 | 14 | 31 | 33 |
| | Hbg | 75 | 9 | 47 | 47 |
| Colon double contrast examination | Ld 1-aut | 110 | 53 | 89 | 90 |
| | Ld 1 | 96 | 38 | | 67 |
| | Ld 1-rap | — | — | | 60 |
| Stomach | Ld-8 | — | | | 37 |
| | Ld-6 | 110 | 5 | 33 | 37 |
| | Ld 5 | 130 | 5 | 29 | 35 |
| | Ld 1-aut | 210 | 8 | 38 | 41 |
| | Ld 1 | 70 | 16 | 30 | 37 |
| | Ld 1 rap | 51 | 5 | 21 | 22 |
| | Ld 7 | 150 | 11 | 25 | 33 |
| | Hbg | 77 | 18 | 31 | 36 |
| Cholecystography | Ld-8 | 37 | 2.6 | 9.3 | 11 |
| | Ld 7 | 35 | 0.7 | 3.5 | 5.7 |
| | Hbg | 62 | 6.2 | 16 | 18 |
| Lungs | Ld-8 | 16 | 1.3 | 5.5 | 6.0 |
| | Ld-6 | 14 | 1.2 | 3.9 | 4.3 |
| | Ld 1-aut | 16 | 1.7 | 4.4 | 5.3 |
| | Ld 1 | 12 | 0.5 | 3.5 | 4.5 |
| | Ld 1 rap | 12 | 1.2 | 2.5 | 3.2 |
| | Hbg | 13 | 4.4 | 7.1 | 7.5 |

integral dose measurements reported under Ld 7 and Ld 1 rap. Normal film was used in Hälsingborg.

Approximate relative exposure times required by standard, normal and rapid films were 1.3, 1.0 and 0.5, respectively.

Standard intensifying ($CaWO_4$) screens with an intrinsic unsharpness of about 0.25 to 0.30 mm were used with the film.

For the fluoroscopy examination ordinary screens (ZnS, CdS) were used except in Ld 7 where the screen was replaced by a 5-inch image intensifier

Table 5 *(cont.)*

| Fluoroscopy | Roentgenograms | Mean dose, rad | Areal exposure, R cm | Roentgenograms per patient | Number of patients | Year for measurements | Voltage, kV Fluoroscopy | Voltage, kV Roentgenograms |
|---|---|---|---|---|---|---|---|---|
| 18 | 39 | 0.7 | 4900 | 10 | 63 | 58—59 | 90 | 100 |
| 22 | 40 | 1.1 | 5200 | 10 | 81 | 59—60 | 90 | 120 |
| 28 | 53 | 0.9 | 4900 | 10 | 26 | 1960 | 90 | 120 |
| 26 | 7 | 0.5 | 2700 | 7 | 20 | 1961 | 90 | 170 |
| 16 | 31 | 0.7 | 5700 | 9 | 19 | 1961 | 80 | 85 |
| 33 | 37 | 0.8 | 7500 | 13 | 14 | 59—60 | 90 | 160 |
| 21 | 43 | 1.1 | 5200 | 18 | 2 | 1960 | 80 | 160 |
| 31 | 29 | 0.8 | 4600 | 16 | 1 | 1961 | 100 | 170 |
| 26 | 11 | 0.5 | 4300 | 9 | 1 | 1960 | 80 | 100 |
| 13 | 23 | 0.3 | 3600 | 11 | 32 | 58—59 | 90 | 100 |
| 25 | 10 | 0.4 | 3600 | 10 | 182 | 59—60 | 90 | 125 |
| 22 | 21 | 0.6 | 3300 | 11 | 211 | 59—60 | 90 | 170—120 |
| 23 | 11 | 0.6 | 2900 | 15 | 30 | 1960 | 90 | 170—120 |
| 18 | 3 | 0.3 | 1700 | 8 | 28 | 1961 | 90 | 170 |
| 24 | 11 | 0.5 | 3500 | 10 | 38 | 1961 | 85 | 125 |
| 18 | 18 | 0.3 | 3100 | 8 | 22 | 1961 | 80 | 95 |
| 6.9 | 4.4 | 0.18 | 1200 | 5 | 66 | 1960 | 90 | 90 |
| 4.0 | 1.8 | 0.08 | 680 | 4 | 36 | 1961 | 80—85 | 80 |
| 6.5 | 12 | 0.27 | 3400 | 6 | 14 | 1961 | 80 | 60 |
| 3.2 | 2.8 | 0.09 | 610 | 4 | 74 | 1960 | 90 | 100 |
| 1.8 | 2.3 | — | 450 | 4 | 67 | 1939 | 80 | 100 |
| 2.9 | 2.5 | 0.05 | 410 | 3 | 108 | 59—60 | 90 | 170 |
| 2.6 | 1.9 | 0.08 | 340 | 4 | 39 | 1960 | 90 | 170 |
| 2.4 | 0.8 | 0.05 | 250 | 3 | 27 | 1961 | 90 | 170 |
| 4.6 | 2.9 | 0.11 | 1400 | 3 | 21 | 1961 | 70 | 90 |

## Results of measurements

As the integral dose measurements have been performed in different examination rooms equipped with varying equipment, the influence of some technical factors, for example, the voltage, might be apparent in the measured results.

The diagnostic problems of the patients vary markedly however and the experience and capacity of the physicians to solve the problems also varies. The latter is of course obvious at a hospital where several physicians are in

**Table 4**

*Integral doses in different examinations*

| Examination | Integral dose kg rad | | | Mean dose rad | Areal exposure R cm | Number of patients |
|---|---|---|---|---|---|---|
| | Total | Fluoroscopy | Roentgenograms | | | |
| Trachea | 3.1 | 2.1 | 1.1 | 0.03 | 270 | 11 |
| Hypopharynx | 8 | 1.5 | 1.3 | 0.03 | 10 | 4 |
| Oesophagus | 13 | 7 | 6 | 0.10 | 1100 | 52 |
| Heart | 7.0 | 3.8 | 3.2 | 0.11 | 670 | 73 |
| Lungs, bedside | 1.7 | — | 1.7 | 0.01 | 170 | 15 |
| Bronchography | 27 | 12 | 15 | 0.37 | 2200 | 2 |
| Cholegraphy | 4.4 | — | 4.4 | 0.07 | 490 | 4 |
| Postoperative cholangiography | 14 | 10 | 4 | 0.19 | 1600 | 6 |
| Small bowel | 1 | 13 | 8 | 0.41 | 1700 | 26 |
| Abdomen | 7.4 | 0.5 | 6.9 | 0.07 | 700 | 66 |
| Urography | 24 | | 24 | 0.33 | 2700 | 67 |
| Pyelography | 16 | 6 | 10 | 0.26 | 2100 | 9 |
| Urethrocystography | 3 | 6 | 26 | 0.35 | 3900 | 16 |
| Hysterosalpingography | 16 | 6 | 10 | 0.23 | 1900 | 21 |
| Pelvimetry | 16 | — | 46 | 0.68 | 4600 | 4 |
| Cervical spine | 1.9 | 0.8 | 1.1 | 0.03 | 200 | 14 |
| Shoulders | 1.3 | | 1.3 | 0.0 | 270 | 11 |
| Thorax | 3.5 | | 3.5 | 0.06 | 530 | 8 |
| Spine, hip and pelvis | 19 | — | 19 | 0.25 | 2000 | 43 |

specialist training. Furthermore, a tendency to transfer certain groups of patients to particular examination rooms or to particular physicians could be observed. In Lund, for example, the examinations in Ld 1 were most often performed by the youngest physicians, while the more experienced roentgenologists worked in Ld 5 and Ld-6. Hence, special cases were often directed

**Table 5**

*Examples of integral doses from simultaneous multisection roentgenography*

| Examination | Exposure value | | No. of tomogram | Integral dose kg rad |
|---|---|---|---|---|
| | kV | mAs | | |
| Sphenoid bone | 115 | 500 | 2 | 4.1 |
| Kidney | 96 | 500 | 1 | 2.8 |
| Kidneys | 91 | 500 | 2 | 3.7 |
| Lung | 115 | 500 | 1 | 1.4 |

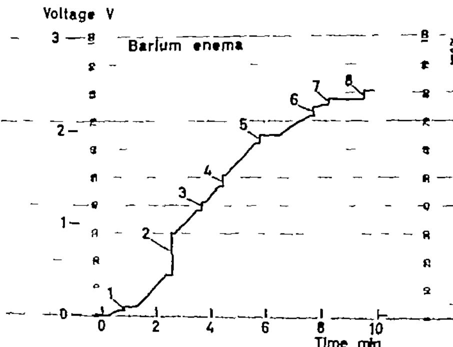



Fig 1 Record of colon examination; fluoroscopy voltage and current were 90 kV 2 mA. Roentgenographic data are given below

| No. | kV | mAs | Film dimension cm | Position of patient | Roentgen tube | Integral dose kg rad |
|---|---|---|---|---|---|---|
| 1 | 120 | 20 | 24 30 | Supine | Undercouch | 1.2 |
| 2 | 120 | 160 | 24 30 | Lateral | | 10 7 |
| 3 | 120 | 40 | 24 × 30 | Oblique | | 2.2 |
| 4 | 120 | 40 | 24 30 | Oblique | | 2.9 |
| 5 | 120 | 32 | 24 30 | Slight oblique | » | 2.3 |
| 6 | 120 | 32 | 24 30 | Slight oblique | | 2.2 |
| 7 | 120 | 25 | 18 24 | Slight oblique | | 1 4 |
| 8 | 170 | 6 | 30 40 | Prone | Overcouch | 2.8 |

to the latter examination rooms. Among the patients of the university hospital in Lund there were, in addition to the ordinary cases of the local hospital a great number of cases that were particularly difficult to diagnose. These patients very often had undergone examinations in other hospitals and were sent to Lund for more detailed examinations.

The results of the measurements are given in Tables 3 to 7 For the more common examinations the results measured in the different examination rooms are separated. Ld I is divided into 3 examination groups Ld I aut

Table 6

*Some examples of integral doses in cineroentgenography*

| Examination | Integral dose kg rad | | | Areal exposure |
|---|---|---|---|---|
| | Total | Fluoroscopy | Cine roentgenography | R cm |
| Oesophagus | 100 | 2 | 99 | 8300 |
| | 53 | 9 | 44 | 5000 |
| | 18 | 3 | 15 | 1500 |
| Hypopharynx | 15 | 5 | 11 | 2100 |
| | 13 | 9 | 4 | 1800 |
| | 7.3 | 6 4 | 0.9 | 790 |
| | 5.3 | 0 3 | 5 0 | 1100 |
| Bronchography | 58 | 4 | 54 | 7100 |
| Kidneys | 22 | 3 | 20 | 2600 |

(with automatic timer and standard film) Ld 1 (without timer with standard film) and Ld 1 rap (without timer with rapid film)

Some of the examinations are commented on in the following section and examples of the records are shown The results of the remaining examinations are compiled in Table 4 Finally some examples from some more unusual examinations are given

*Colon* (*barium enema*) In a colon examination the contrast medium was introduced in the colon during fluoroscopy with an undercouch tube Roentgenograms were obtained with the same tube Usually at least one roentgenogram (a survey) was taken with an overcouch tube. Fig 1 shows a record of an integral dose measurement (Ld 1) (The voltage and current for the fluoroscopy of the examination shown in Fig 1 were 90 kV and 2 mA for the roentgenograms see Fig 1 ) The record is redrawn in order to show a positive time axis. The ordinate in Fig 1 the voltage across the condenser is approximately proportional to the areal exposure measured in R cm² The integral dose can be calculated from the graph as reported in part I of this article (CARLSSON 1965) The relative contribution of the roentgenograms to the integral dose will then be about 1 4 times greater than indicated in Fig 1 The integral dose from this examination was 50 kg rad the fluoroscopy giving 24 kg rad and the roentgenograms 26 kg rad

Table 3 gives integral doses measured in the different examination rooms

Table 7

*Some examples of integral doses in angiographic examinations*

| Examination | Integral dose, kg rad | | | Mean dose rad | Areal exposure, R cm | No. of roentgenograms |
|---|---|---|---|---|---|---|
| | Total | Fluoroscopy | Roentgenograms | | | |
| Cavography | 75 | 16 | 59 | 1.1 | 7700 | 94 |
| Nephroangiography | 28 | 13 | 15 | 0.38 | 3100 | 24 |
| | 28 | 7.8 | 20 | 0.52 | 3000 | 41 |
| | 80 | — | 80 | 0.91 | 7300 | 41 |
| Pulmonaryangiography | 80 | 26 | 54 | 1.0 | 8300 | 84 |
| Splenoportography | 41 | — | 41 | 0.62 | 4300 | 20 |
| | 18 | — | 18 | 0.30 | 2100 | 12 |
| Pelvic angiography | 64 | 21 | 43 | 1.1 | 6300 | 31 |
| Angiography of the subclavian artery | 13 | 3.8 | 9.1 | 0.27 | 1700 | 48 |
| Angiocardiography | 75 | 3.9 | 71 | 1.1 | 6700 | 110 |
| | 36 | 8.0 | 28 | 1.0 | 5400 | 86 |
| | 36 | 19 | 17 | 2.3 | 5900 | 86 |
| | 44 | 24 | 20 | 4.4 | 5200 | 108 |

(see Table 2). Maximum, minimum, median, and mean values are given in addition to mean values from fluoroscopy and roentgenograms, respectively. As the patients were not always weighed, the average of the mean dose is often calculated from a smaller number of patients than the corresponding average of integral dose.

The very low integral dose shown by the roentgenograms in Ld 1-rap (about a factor of 5 lower than from the other examination rooms) was mainly caused by (1) more sensitive film, (2) higher voltage, 170 kV for all the roentgenograms (see Tables 2 and 3), and (3) a smaller number of roentgenograms (Table 3).

Fig. 2 shows how the mean value of integral dose varied in each examination room for the different physicians. In some cases the number of measured examinations was small. Therefore the results in Fig. 2 can not always be regarded as characteristic for the physician. By evaluating the integral doses given by a physician when working in different examination rooms, the effect of the technical factors on the integral dose would be more distinct. It must be noted, however, that during the time between the measurements in different

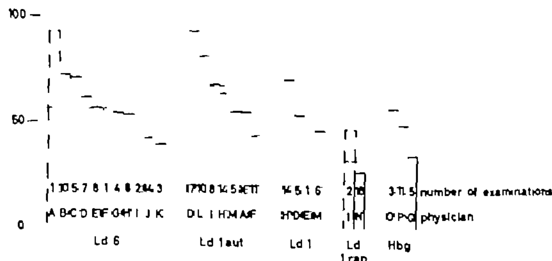



Fig 2 Integral doses in colon examinat ons. Mean values are gi en for each physicia in each examination room. When only on or two examinations re included the bars are dotted.

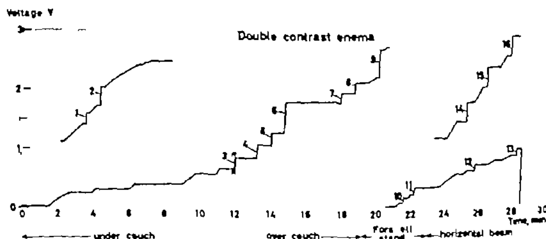



Fig 3 Record of colon examination (doubl contrast study) First part of examinat on in the left insert the right nsert is n example from nother examination with n filter on the roentgen t be.

examinations rooms (sometimes about 2 years) a physician may improve his diagnostic ability For the young physicians there was an obvious decrease of integral doses with increased experience

Fig 2 and Table 4 show that the mean value of the integral dose did not vary appreciable in Ld-6 Ld 1 aut and Ld 1 whereas Hbg showed a lower value, and Ld 1 rap showed a considerably lower value

The maximum value, given in Table 4 is 400 kg rad This corresponds to a mean absorbed dose of 3 3 rad and considerably higher local doses and was

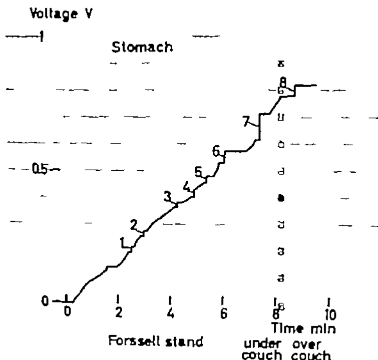



Fig. 4. Record of examination of stomach. Fluoroscopic data 80 kV 2 mA. Roentgenographic data

| No. | kV | mAs | Film dimension cm² | Roentgen tube | Integral dose, kg rad |
|---|---|---|---|---|---|
| 1 | 170 | 5 | 13 18 | Forssell stand | 0.5 |
| 2 | 170 | 5 | 13 18 | Forssell stand | 0.5 |
| 3 | 170 | 5 | 13 18 | Forssell stand | 0.4 |
| 4 | 170 | 8 | 13 × 18 | Forssell stand | 0.8 |
| 5 | 170 | 8 | 13 × 18 | Forssell stand | 0.7 |
| 6 | 170 | 4 | 24 × 30 | Forssell stand | 1.3 |
| 7 | 120 | 25 | 24 30 | Undercouch | 2.4 |
| 8 | 170 | 6 | 24 30 | Overcouch | 1.3 |

measured with a patient weighing 120 kg In this case the detailed analysis of the complicated pathologic process (a vesico-colic fistula) by a rather inexperienced examiner is the explanation of the high dose

*Colon* (*double contrast examination*) In this examination a smaller amount of contrast medium was injected into the colon during fluoroscopy than in the ordinary colon examination. Usually a few roentgenograms were then taken

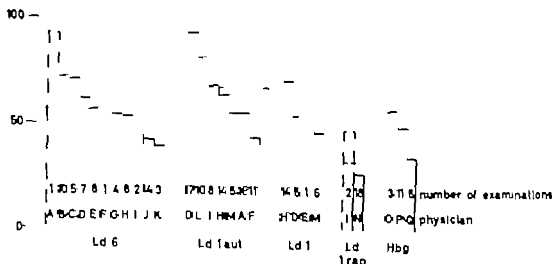



Fig 2 Integral doses in colon examinations Mean values are given for each physician in each examination room When only one or two examinations are included the bars are dotted

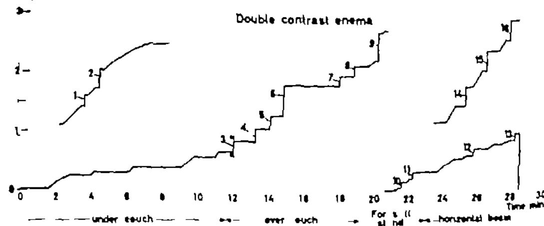



Fig 3. Record of colon examination (double contrast study) First part of examination in the left insert the right insert is an example from another examination with no filter on the roentgen tube

examinations rooms (sometimes about 2 years) a physician may improve his diagnostic ability For the young physicians there was an obvious decrease of integral doses with increased experience

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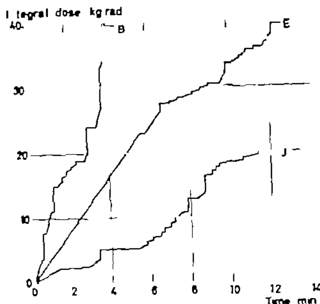



Fig 6. Typical examples of examination techniques of three different physicians. B was careless with the use of the diaphragm but swift in fluoroscopy E used the diaphragm carefully but fluoroscopy rather long time. J is one of the physicians with the lowest integral doses administered (cf Figs 2 and 3)

**Stomach** (*barium examination*) In a stomach examination the patient was examined both recumbent and standing by means of alternating fluoroscopy and roentgenograms. In Ld-5 and Ld 7 the whole examination was performed with the same roentgen apparatus, a universal stand. In the other examination rooms the patient was examined in the recumbent position, with undercouch and overcouch tubes, and standing on a Forssell stand. In the latter case a focus-film distance of about 75 cm was used

Fig 4 shows the record of an examination of a normal patient weighing 48 kg The fluoroscopy was performed with a voltage of 80 kV and a current of 2 mA, and most of the roentgenograms were taken with 170 kV and 5 to 8 mAs. The integral dose in this examination was 17 kg rad (9 kg rad from fluoroscopy and 8 kg rad from the roentgenograms)

Table 3 gives the results of the measurements, while Fig 5 shows how the mean value of the integral doses varied with the different physicians in different examination rooms.

In Ld-5 and Ld 7 they usually exposed several well coned roentgenograms on the same 24 × 30 cm film. In the other examination rooms the smallest




Fig 5 Integral doses in stomach examinations Mean values are given for each physician in each examination room

(two roentgenograms, 1 and 2 in Fig 3 left insert) After the patient had evacuated air was pumped into the colon during fluoroscopy dispersing the remaining contrast medium in a thin layer on the wall of the colon A series of roentgenograms were then taken with the overcouch tube (3 to 8 in Fig 3) The patient was then examined (standing on the Forssell stand) by means of fluoroscopy and roentgenograms (9 to 11 in Fig 3) At least the patient lying on his side was examined with a horizontal beam (12 to 13 in Fig 3) Coning of the latter roentgenograms was often done by using fluoroscopy as in Fig 3 This was, however not necessary as the adjustment could be made by means of the light localizer thereby reducing the doses to the patient and especially to the physician

The right insert in Fig 3 14 to 16 shows a record from an earlier examination of the same type before the horizontal beam tube had been supplied with filter (see Table 2) With the decrease of the areal exposure due to the filter obvious from Fig 3 there is a corresponding but lesser decrease of the integral dose

Roentgenogram 9 in Fig 3 was overexposed due to an error in choosing the mAs value (170 kV 63 mAs instead of 170 kV 10 mAs) and was immediately retaken as No 10

The examination shown in the record of Fig 3 gave 120 kg rad for the integral dose of which about 40 kg rad was due to fluoroscopy and 80 kg rad to the roentgenograms

The results of the measurements are given in Table 3 In these examinations the roentgenograms gave a contribution to the integral dose almost twice as large as the fluoroscopy Therefore the change to a more sensitive film (Ld 1 rap) considerably reduced the radiation doses.

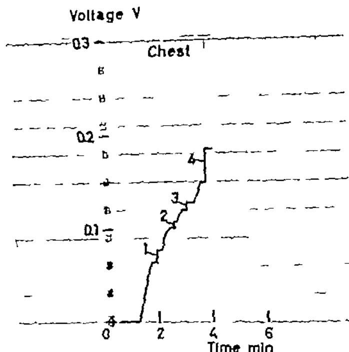



Fig. 8. Record of lung examination. Fluoroscopic data: 90 kV 2 mA and 2.2 kg rad. Roentgenographic data: 170 kV 5 to 10 mAs.

ent from the records. Fig. 6 shows as typical examples how the integral dose increased during the examination for 3 different physicians *B*, *E* and *J*. Physician B worked very swiftly and used fluoroscopy only for short times but was careless with the diaphragms. E often started his examinations with a rather long fluoroscopy time and a relatively large field; he then finished the examination properly using the diaphragms. J belonged to the physicians with the lowest integral doses (cf. Figs 2 and 5).

*Cholecystography.* Cholecystography was performed with both fluoroscopy and roentgenograms and with the patient both standing and lying. Fig. 7 shows a record of a gallbladder examination from Hälsingborg. The integral dose in this case was 14 kg rad (2 kg rad from fluoroscopy and 12 kg rad from the roentgenograms). The Forssell stand used in this examination had no filter which partly explains the high areal exposure values measured in Hälsingborg (see also Table 3).

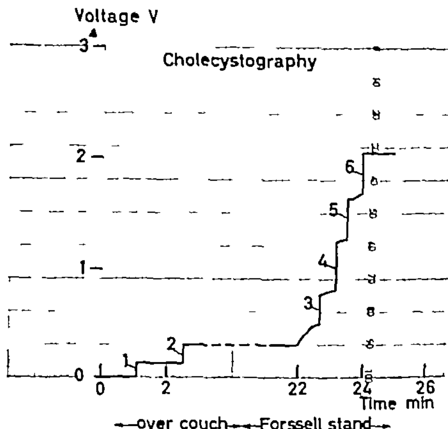



Fig. 7. Record of examination of gallbladder. Fluoroscopic data 60 kV 2 mA; roentgenographic data 65 kV 300–400 mAs, 24 × 30 cm. No filter on the tube of the Forssell stand.

film size used was 13 × 18 cm². In Ld 1 aut the beam cross section in the film plane could not be made smaller than 13 × 13 cm owing to the lack of sensitivity of the automatic timer. Some random tests of the field area of roentgenograms of the duodenal bulb show that the field was seldom smaller than the film (exceptions Ld 5 and Ld 7), that is, the physician chose the field in relation to the film size rather than to the organ to be examined.

In Fig. 5 and Table 3 no great difference can be detected between Ld-6, Ld 5, Ld 1, Ld 7 and Hbg, whereas Ld 1 aut shows significantly higher integral doses. This can be explained at least partly by the automatic timer, which absorbed radiation and required a field size larger than 13 × 13 cm². Rapid film was used in Ld 1 rap and Ld 7. Ld 1 rap shows low integral-dose values while the higher values from Ld 7 are misleading because of the statistical dominance of a visiting physician apparently unfamiliar with the ordinary technique.

The various examination techniques used by different physicians are appar

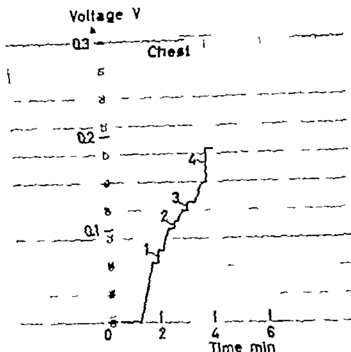



Fig. 6. Record of lung examination. Fluoroscopic data 90 kV mA and 2.2 kg rad. Roentgenographic data 170 kV 3 to 10 mAs.

ent from the records. Fig 6 shows as typical examples how the integral dose increased during the examination for 3 different physicians B E and J Physician B worked very swiftly and used fluoroscopy only for short times but was careless with the diaphragms. E often started his examinations with a rather long fluoroscopy time and a relatively large field he then finished the examination properly using the diaphragms. J belonged to the physicians with the lowest integral doses (cf. Figs 2 and 5)

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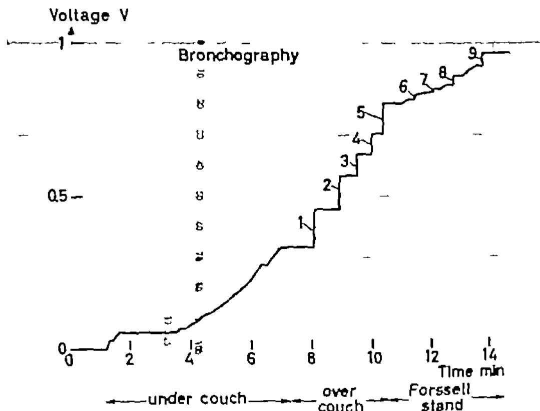



Fig. 9 Record of bronchographic examination.

*Lungs and heart* The examination of the lungs was mainly performed in a Forssell stand (FFD = 150 cm) One roentgenogram was taken in the posterior anterior and one in the lateral projection Sometimes the examination was extended in order to take small roentgenograms of the apices of the lungs or to take one or two roentgenograms of the recumbent patient with a horizontal beam

Fig 8 shows one example of a lung examination with an integral dose of 4 2 kg rad of which 2 2 kg rad came from fluoroscopy and 2 0 kg rad from the roentgenograms.

Table 3 gives the results of the measurements roughly showing decreasing integral doses from the roentgenograms with increasing tube voltage

The heart examination included the lungs Therefore no great difference between heart and lung examinations could be noted in the integral-dose records The roentgenograms of the heart were however more exposed In Table 4 the results from the heart examinations are given

The estimation of a patient as equivalent to a 20 cm thick water slab is apparently not valid when the chest is irradiated because of the transparency

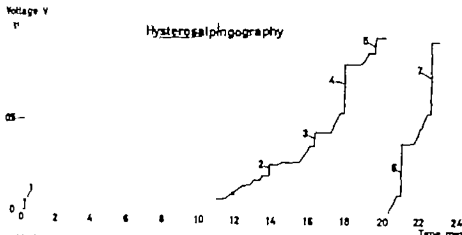



Fig. 10. Record of hysterosalpingography. Fluoroscopy was performed with 90 kV 2 mA, the roentgenograms obtained with 83 kV 30 to 400 mAs.

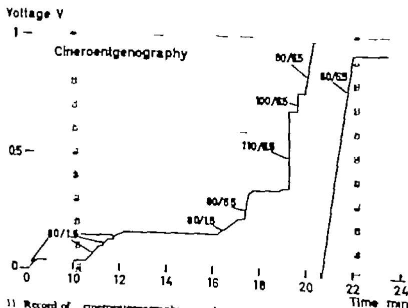



Fig. 11. Record of cineroentgenographic examination of kidneys. Fluoroscopic data (80 kV 1.5 mA) and cineroentgenographic data (80 to 110 kV 6.5 mA) are indicated in the figure.

of the lungs. Because of this transparency and the fact that radiation passes outside the patient, the results given (Tables 3 and 4) may be falsely high by about 15 to 20 This is also true for some other chest examinations, for example bronchography

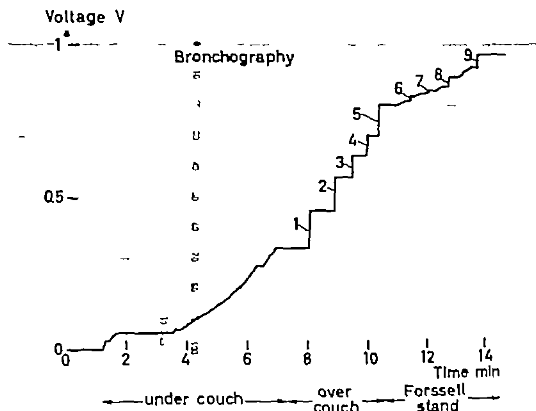



Fig 9 Record of bronchographic examination.

*Lungs and heart* The examination of the lungs was mainly performed in a Forssell stand (FFD = 150 cm) One roentgenogram was taken in the posterior anterior and one in the lateral projection Sometimes the examination was extended in order to take small roentgenograms of the apices of the lungs or to take one or two roentgenograms of the recumbent patient with a horizontal beam

Fig 8 shows one example of a lung examination with an integral dose of 4 2 kg rad of which 2 2 kg rad came from fluoroscopy and 2 0 kg rad from the roentgenograms.

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The estimation of a patient as equivalent to a 20 cm thick water slab is apparently not valid when the chest is irradiated because of the transparency

ities are omitted because of the large fraction of the radiation that passes outside the patient, and because the thickness of these body parts varies too much for the use of a standard calibration value.

*Body section roentgenography* A few examples of integral doses from simultaneous multisection roentgenography are given in Table 5 A cassette with up to 7 film-screen combinations was used in the examinations. The relatively low integral doses measured may be explained by small beam cross sections, rapid film, and fast screens.

*Cineroentgenography* A few integral-dose measurements from cineroentgenographic examinations were made. In these examinations the screen of a 5-inch image intensifier was photographed with a cine-camera using 35 mm film. The results are given in Table 7 An example of a record of a cineroentgenographic examination of the kidneys is shown in Fig 11 The fluoroscopy data were 80 kV and 1.5 mA, and the cineroentgenography data were 80 kV and 6.5 mA. In an attempt to find appropriate exposure data for the cineroentgenography some higher values than given above were tried (see Fig 11)

*Serial roentgenography* In angiographic examinations a biplane film changer for full-size roll film was used together with rapid film and fast screens. Some examples from the integral-dose measurements are given in Table 7 Fig 12 shows a record from a splenoportography The two first roentgenograms are taken with 80 kV and 190 mAs, the following series with 100 kV and 50 mAs. The time intervals were 1 sec between the first 12 roentgenograms and 3 sec between the 6 following In Fig 13 an angiocardiographic examination with a series of 110 roentgenograms is shown

## Comparison with other measurements

Results from measurements of integral dose or areal exposure in roentgendiagnostic examinations have been reported by FEDDEMA & OOSTERKAMP (1953) GOLDMAN LORENZ & WOLF (1960) REINSMA (1960—1962) SANCHES (1961) ARMAL & PYCHLAU (1961 and 1962) SCHOEN & GRIESSER (1964) BIRZLE & OERTMANN (1964) Some of these results are collected in Table 8.

A comparison of the results from the present material with those reported by the above mentioned authors may be rather difficult. The values given by FEDDEMA & OOSTERKAMP seem to be determined in a manner similar to that used by the present author REINSMA neglects the escape energy and equates the integral dose to the incident energy thereby causing an overestimation of

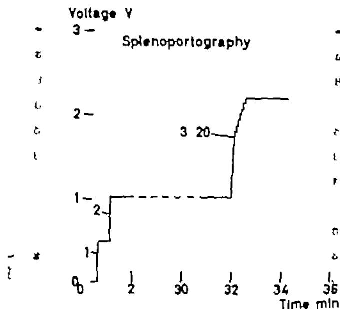



Fig 12 Record of splen portography No fluoroscopy was used; th tw first roentgenograms were exposed with 80 kV 190 mAs, the following series (18 roentgenograms) with 100 kV 30 mAs.

*Bronchography* An example of this examination is given in Fig 9 The patient was examined in the recumbent position with undercouch and overcouch tubes and standing on the Forssell stand (in the latter case with FFD = 150 cm) The integral dose was 21 kg rad of which fluoroscopy gave 7 kg rad and the roentgenograms 14 kg rad Results from the measurements are given in Table 4

*Urography* This examination was performed with roentgenograms only The results are given in Table 4 and an example of how the integral dose is distributed in time is included in Fig 14

*Hysterosalpingography* In the example shown in Fig 10 the integral dose was 25 kg rad with 9 kg rad from fluoroscopy and 16 kg rad from the roentgenograms For roentgenograms Nos. 4 and 6, two secondary radiation grids (cross grids) were used to improve the image quality For roentgenogram 7 rapid film was used whereas standard film was used for the other roentgenograms. The results from the measurements are given in Table 4

*Skeleton* Results from some skeleton examinations are given in Table 4 The examinations are collected in three groups shoulders thorax and spine including the pelvis. Integral-dose measurements from examinations of the extrem

Table 8 *(cont.)*

| [illegible] (9-inch image intensifier) | Gollin et coll. | [illegible] et coll. | [illegible] et coll. | Arnal et coll. | Present report |
|---|---|---|---|---|---|
| 16 | 110 | — | — | — | 59 |
| — | — | 7300 | 9200 | 8400 | 4900 |
| 7.5 | 70 | — | — | — | 38 |
| — | — | 3500 | — | 6700 | 3400 |
| 2.0 | — | — | — | — | 10 |
| — | — | 860 | — | 1200 | 1300 |
| 0.8 | 5 | — | — | — | 5.0 |
| — | — | 390 | — | 440 | 500 |

elaborating diagnostic techniques, and (f) as an aid in the training of new roentgenologists. Furthermore, integral dose measurements undoubtedly stim ulate an increased interest in radiation protection.

In the present study too many parameters varied simultaneously for a proper determination of the influence of an individual parameter on the integral dose. For example the decrease of the integral dose due to higher voltage was in this study reduced by the use of the automatic timer  which increased the exposure and necessitated a rather large field. Even the wide range of film density

Table 9

*Fraction (%) of the integral dose due to the roentgenograms*

| Examination | Lund | | Hbg normal film | [illegible] |
|---|---|---|---|---|
| | Standard film | Rapid film | | |
| Colon | 62 | 21 | 66 | 33 |
| Colon, double contrast | 59 | 48 | — | — |
| Stomach | 40 | 28 | 50 | 30 |
| Cholecystography | 40 | 32 | 67 | 33 |
| Oesophagus | 45 | 19 | 52 | 56 |
| Lungs | 49 | 23 | 39 | 0 |
| Heart | 52 | 20 | 29 | 0 |
| Bronchography | 39 | 40 | — | 12 |
| Hysterosalpingography | 71 | 61 | — | 21 |

**Table 8**

*A comparison of results of other authors with this report*

| Examination | Measured quantity | Feddema et coll. | Reinsma |
|---|---|---|---|
| Colon | Integral dose kg rad | 51 | 66 |
| | Areal exposure R cm | — | — |
| Stomach | I d. kg rad | 21 | 27 |
| | A e. R cm | — | |
| Gallbladder | I.d. kg rad | 6.7 | 7.4 |
| | A R cm | — | — |
| Chest | I d kg rad | 11 | 4.2 |
| | A.e R cm | — | — |

the integral dose His presumption that the energy fluence necessary to produce 1 R in air is the same for a roentgen spectrum as for monoenergetic photons with the same HVT causes an underestimation of the incident energy of the roentgen radiation this underestimation becomes more marked for a lower filtration (Carlsson 1963) The net result will however give average integral dose values not differing more than about + 25 % from those determined according to methods used in this article

Sanches used the same method and equipment as Reinsma. They have to a great extent collaborated and published the same integral-dose values In Table 8 therefore only Sanches measurements of integral doses with a 9-inch image intensifier are reported

In the present study the fraction of the integral dose due to roentgenograms was about 50 % with standard or normal film and about 30 % with rapid film (Table 9) For comparison Reinsma and Sanches report only about 30 % with normal film

## Conclusions

Integral dose measurements like those now presented may be of value (a) for obtaining knowledge of the average integral doses delivered to patients in different examinations, (b) for studying the distribution of the integral dose at different times during the examination (c) in comparing the influence of different technical factors on the integral dose (d) in charting an examination in order to be able to reconstruct it in phantom experiments, (e) for

## SUMMARY

With large plane-parallel ionization chambers (monitors) placed between the adjustable diaphragms of the roentgen tube and the patient, measurements of integral absorbed dose in some roentgendiagnostic examinations have been performed. The monitors were mounted on 23 roentgen tubes in tw hospitals. Tables with the results of about 2 000 integral dose measurements are given. Twenty-five physicians performed the roentgen examinations. How the integral dose is distributed at different moments during the examination is effectively revealed by the records, of which several examples are given. The records also show the diagnostic methods used t these departments. Finally the integral dose measurements are compared with those of other authors.

## ZUSAMMENFASSUNG

Mit grossen planparallelen Jonisationskammern (Monitore) die zwischen den adjustierbaren Blenden der Röntgenröhre und dem Patienten angebracht waren, wurden Messungen an absorbierten Integraldosen bei einigen röntgendiagnostischen Untersuchungen durchgeführt. Die Monitore waren an 23 Röntgenröhren in insgesamt zwei Krankenhäusern angebracht. Es werden Tabellen mit den Resultaten von ungefähr 2000 I tegraldosenmessungen wiedergegeben. Die Untersuchungen wurden on 25 Ärzten ausgeführt. Die Art der Vertei lung der Integraldosis zu verschiedenen Zeitpunkten der Untersuchung geht genau us den Aufzeichungen hervor wovon einige Beispiele gegeben werden. Es geht auch daraus hervor welche diagnostischen Methoden an diesen Abteilungen zur Anwendung kamen. Schliesslich wurden die Integraldosenmessungen mit denen anderer Autoren verglichen.

## RÉSUMÉ

Des mesures de dose intégrale absorbée au cours de certains examens radiologiques ont été faites au moyen de grandes chambres d'ionisation à électrodes planes parallèles placées entre le diaphragme églable du tube et le malade. Ces chambres ont été montées sur 23 tubes dans deux hôpitaux. Des tableaux donnent les résultats d environ 2 000 mesures de dose intégrale. Les examens radiologiques ont été faits par 25 médecins. Les enregistrements, dont des exemples son donnés, révèlent effectivemen la distribution de dose intégrale à divers moments au cours des examens. Ils montrent aussi les méthodes diagnostiques utilisées dans ces services. Enfin, ces mesures de dose intégrale sont comparées avec celles faites par d' utres uteurs.

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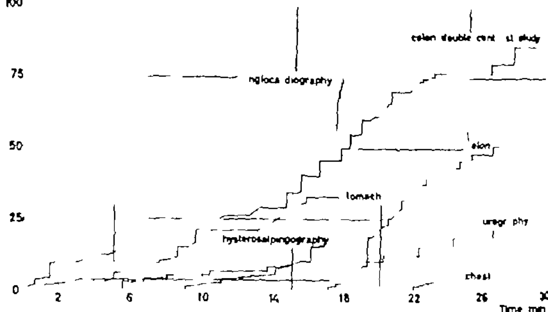



Fig 13 Measured integral doses from som different roentgendi gnostic ex m nations.

(approximately a factor of 2) giving acceptable roentgenograms may mask the influence of technical parameters.

SANCHES (Table 8) reported very low integral doses when using a 9-inch image intensifier but more ordinary dose levels with a 5-inch image intensifier The latter findings are in agreement with the present examination

An approximate summary of the measurements is given in Fig 13 which *shows how the integral dose increases with time for different* examinations. The examples given in Fig 13 are approximate median values.

Permanently mounted monitors can be useful tools in a roentgendiagnostic department Universal stands are especially convenient for integral-dose measurements, since complete examinations are performed with only one roentgen tube and no field illumination is used in these units

Changes in technology of apparatus and examination technique are rapid Therefore if the integral dose results are to be used for epidemiologic investigations the measurements should be carried out continually or at intervals short enough to note the effects of changing techniques

## Acknowledgements

I wish to express my sincere gratitude to Professors Kurt Ladén and Olle Olsson for valuable discussions and continuous encouragement and to Yngve Na ersten and Olle Elung for valuable help w th the measurements. The investigation was supported by grants from the Swedish Cancer Society and the Swedish Medical Research Council

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# INTRAARTICULAR TREATMENT WITH COLLOIDAL $^{198}$Au OF PERSISTENT SYNOVIAL EFFUSION IN THE KNEE

## Preliminary report

by

L. Gynning, O. Odelberg-Johnson, B. Waldeskog and Bo Wendeberg

Persistent synovial effusion of the knee joints is a common, painful and immobilizing symptom in cases of osteoarthritis and rheumatoid arthritis. It is usually conservatively treated with aspirations, intra-articular injection of cortisone and radiotherapy or, as a last resort, with synovectomy. The synovium shows in these conditions inflammatory reaction, which is held responsible for the increased amount of fluid in the joint. Irradiation of the knee suppresses this inflammatory reaction and thereby reduces the amount of fluid. A disadvantage of external roentgen irradiation is that both the skin and the tissue in the immediate surroundings of the joint receive a relatively large roentgen dose. It would be an advantage if the synovium could be irradiated from within by a beta radiating isotope deposited directly in the knee joint and with affinity to the synovial layer. The treatment would thus

From the Departments of Radiotherapy (Director: Inge Gynning), Orthopedic Surgery (Director: Sophus von Rosen) and Pathology (Director: Folke Linell), Malmö General Hospital, Sweden. Submitted for publication 11 December 1964.

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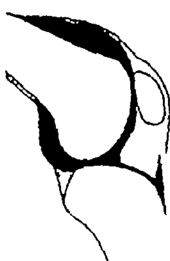


Fig. 1. Section of knee with joint capsule and anterior upper and posterior recesses.

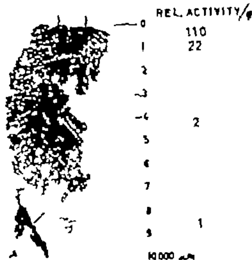



Fig. 2. Cylinder of tissue stamped from knee joint with relative activity at different depths. Detail in frame — see fig. 3.

*Material.* The material consisted of 19 patients (14 females and 5 males) aged 38 to 73 (Table 1). Two of the patients were treated for effusion of both knee joints and the material thus consisted of 21 treated joints. In 10 of these the synovitis was due to osteoarthritis and in 9 to rheumatoid arthritis. In all of these 9 joints the diagnosis was confirmed serologically. Fluid usually had repeatedly been aspirated from the joints before treatment.

*Anatomy.* Fig. 1 shows a knee joint in cross section with the joint capsule and the anterior upper and posterior recesses. This figure should be compared to the lateral scintigrams in Fig. 4. The cartilaginous articular surface area is enclosed in a fairly large joint cavity bordered by the joint capsule, the inner surface of which is lined by mesothelium, the synovium; the surface of the latter may be increased by villous proliferation. The joint cavity normally contains only a very small amount of fluid which is a filtrate of the blood plasma.

*Method.* Under sterile precautions all synovial fluid was aspirated (Record No. 20 needle) from the knee joint to be treated, and 5 mCi of colloidal $^{198}$Au in 20 ml physiologic saline injected through the same needle. The activity used was chosen after a relatively rough estimation of the synovial surface as being about a twentieth of a unilateral pleural surface. (In the treatment of pleural

Table 1

*Case material (19 patients) treated with colloidal $^{198}$Au injected into the knee joints ([illegible]1 joints)*

| Sex and Age | Diagnosis | | Number of aspirations | | | |
|---|---|---|---|---|---|---|
| | Local | Generalized | Before injection | Joint | After injection | |
| | | | | | 0—8 weeks | > 8 weeks |
| ♀ 49 | | *Rheumatoid arthritis* | > 25 | L | 0 | 0 |
| | | | > 25 | R | 0 | 0 |
| ♀ 7 | Osteoarthritis | | > 50 | L | 4 | 1 |
| | | | | L | 1 | 2 |
| | | | 50 | R | 2 | > 8 |
| | | | | R | 2 | 2 |
| ♀ 59 | Osteoarthritis | | 10 | L | 1 | 2 (after trauma) |
| 75 | Posttraum. a. d. | | 14 | R | 2 | 1 |
| ♀ 65 | Osteoarthritis | | > 10 | L | 0 | 0 |
| ♀ 54 | | *Rheumatoid arthritis* | 42 | L | 2 | 0 |
| ♀ 56 | Osteoarthritis | | 7 | R | 1 | 0 |
| ♂ 60 | | *Rheumatoid arthritis* | > 50 | R | 2 | 0 |
| ♀ 50 | Osteoarthritis | | 7 | R | 1 | 0 |
| ♀ 60 | Osteoarthritis | | 10 | R | 1 | 0 |
| ♀ 60 | | *Rheumatoid arthritis* | > 10 | I | 1 | 0 |
| ♀ 48 | | *Rheumatoid arthritis* | 10 | J | 1 | 0 |
| ♂ 67 | Osteoarthritis | | 10 | R | 3 | 1 |
| | | | | R | 1 | 0 |
| ♀ 63 | | *Rheumatoid arthritis* | 20 | L | 2 | 10 |
| ♀ 38 | Osteoarthritis | | 3 | R | 1 | 0 |
| ♂ 43 | | *Rheumatoid arthritis* | > 10 | R | 1 | 0 |
| ♂ 55 | Osteoarthritis | | 10 | L | 1 | 0 |
| ♀ 60 | | *Rheumatoid arthritis* | 30 | R | 1 | 0 |
| ♂ 59 | | *Rheumatoid arthritis* | 20 | R | 1 | 1 |

resemble that given to patients with effusion of fluid into the pleural and peritoneal cavities in which promising results have been obtained during the 1950s on treatment with colloidal $^{198}$Au (MÖLLER 1950 HANSEN 1960 and others)

As early as 1950 LOW BEER stated that experimental studies by BERTRAM TOBIAS, AINE et coll indicated a high uptake of gold by reticulo-endothelial cells of synovial membranes and showed that the bulk of colloidal Au injected into the knee joint is concentrated in the synovium This prompted the present authors in 1961 to study the effect of internal irradiation of knees with persistent effusion Colloidal Au was injected directly into the knee joint

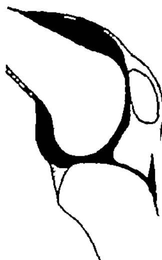


Fig 1 Section of knee with joint capsule and anterior upper and posterior recesses.

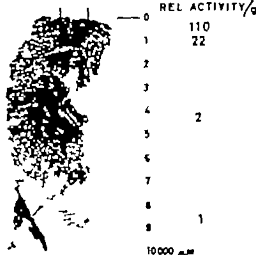



Fig 2 Cylinder of tissue stamped from knee joint with relative activity at different depths Detail in frame — see fig 3.

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*Method* Under sterile precautions all synovial fluid was aspirated (Record No. 20 needle) from the knee joint to be treated, and 5 mCi of colloidal $^{198}$Au in 20 ml physiologic saline injected through the same needle. The activity used was chosen after a relatively rough estimation of the synovial surface as being about a twentieth of a unilateral pleural surface (In the treatment of pleural



Fig. 3. Microscopy of tissue cylinder from the synovium. A thin mesothelial layer with accumulations of gold particles lies above, and loose connective tissue with vascular spaces below. Entire depth 750 $\mu$m.

effusion an activity of 75 to 125 mCi is generally used.) The knee joint was immobilized with an elastic bandage and the patient was instructed to rest for 24 hours. Frontal and lateral scintigrams were obtained for checking the distribution of the activity within the knee joint 24 hours after injection. A control scintigram over the regional lymph nodes in the groin and over the liver was obtained in about two-thirds of the patients. The same measuring procedures were repeated after one week. In all instances except one the joints have been completely emptied three weeks after the injection of $^{198}$Au in order to obtain basic values for the evaluation of persistent effusion of synovial fluid. The patients were afterwards examined once a month for the next 3 months and then at 6 monthly intervals with special reference to pain, effusion and mobility.

In order to estimate the leakage to regional lymph nodes and liver as well as the distribution of the activity in the knee joint, 1 mCi of $^{198}$Au was injected into a normal knee joint of a moribund patient. Two days after the injection the entire knee joint, lymph nodes from the right groin and liver tissue were removed at autopsy for examination. A cylinder piece of tissue 10 000 $\mu$m long was punched out from the opened knee joint and comprised all layers from the synovial membrane down to the underlaying bone tissue. The cylinder was cut longitudinally into two halves: one half was embedded for microscopic

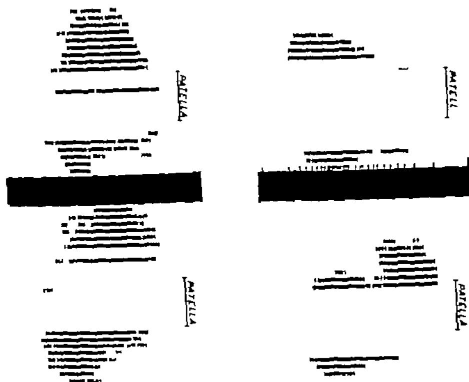



Fig 4 Frontal (upper) and lateral (lower) scintigrams one day after injection of 5 mCi $^{198}$Au of knee with effusion (left) and synovectomized knee with effusion (right)

examination, while the other half was used for determination of radioactivity in different transverse layers (Fig 2)

## Results

*Normal knee* The relative activity per gram of tissue of the synovial membrane was 6 700 the corresponding values for extirpated lymph node and liver tissue being 9 and 1 respectively

The distribution of the activity within the cylinder of tissue is given in Fig 2 from which it is evident that the relative activity per gram of tissue of the synovial layer was 110 that of the capsule layer 22, that of the connective

tissue 2 and that of osseous tissue 1 There is probably a steep activity gradient within the synovial layer

Microscopic examination (F Linell) revealed abundant gold particles in the upper thin mesothelial layer but only few in the underlaying loose connective tissue (Fig 3)

*Knee with persistent effusion* Fig 4 shows the frontal and lateral scintigrams over the knee joint one day after the injection of 5 mCi $^{198}$Au in an unoperated patient with synovitis and of one patient who had previously undergone synovectomy It is clear from the figure that the activity at the site of the upper recess was much lower in the second patient

The results of the evaluation of leakage are given in Fig 5 which shows a total scintigram one day after injection of the isotope It is evident from the figure that leakage to the regional lymph nodes and liver was relatively slight Of the 14 patients studied for leakage seven presented roughly the same appearances while in the remaining seven patients no leakage was evident

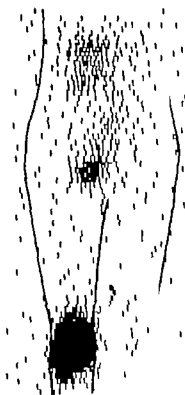


Fig 5 Examination for leakage to groin and liver one day after injection of 5 mCi $^{198}$Au.

Fluid was aspirated on the 10th day in one patient with marked increase of the joint fluid after injection of the isotope The fluid aspirated contained 3% of the activity of the dose injected and comparison of the scintigrams before and after aspiration of the fluid revealed no measurable difference in the distribution of the activity *This means that the isotope is well bound to the synovium soon* after the intraarticular injection

The results of treatment are given in Table 2 In 13 joints the effusion disappeared after the first injection and in 12 of them within 8 weeks. The joint in the remaining 5 patients still contained fluid but not in such quantities as to require aspiration Three of these patients were symptom free and were carrying on their usual work in the remaining two patients in this group it was some coexisting disease that prevented them from returning to their former activities. Only slight or even no improvement was noted in 3 patients and in these the treatment was repeated An amount of 3 mCi of $^{198}$Au were then injected in two of the patients and 5 mCi in one The second injection of $^{198}$Au

Table 2

*Results of treatment by injection of the knee joint with colloidal ¹⁹⁸Au*

| Injection | Number of joints | No effusion after 8 weeks | No effusion after 4 months | Persistent slight effusion | No effect |
|---|---|---|---|---|---|
| First | 21 | 12 | 1 | 5 | 3 |
| Second | 3 | 1 | — | 1 | 1 |

resulted in freedom of symptoms within 8 weeks in one patient, persistent slight effusion in one, although not as much as to require aspiration, and no improvement in one patient. The patients have been followed up for from 6 months to more than 3 years between 0.5 and 1 year for 4 joints, 1—2 years for 5 joints, 2—3 years for 10 joints and more than 3 years for 2 joints.

## Discussion

MAKIN et coll. (1963) reported the results of treatment of 9 patients with persistent synovial effusion of knee joints, all the patients being given a single intraarticular injection of 10 mCi ¹⁹⁸Au. The effusion disappeared within 8 weeks in 8 of these patients. The patients were followed up for from 8 months to 4 years, during which no recurrence was noted. The pain usually disappeared in association with the effusion.

In the present material 21 knee-joints were treated with 5 mCi ¹⁹⁸Au, which resulted in freedom of symptoms in 13 and slight persistent effusion not requiring re-punction in 5 joints The effect of administration of 5 mCi ¹⁹⁸Au in a single injection was thus satisfactory in 18 of the 21 joints treated. In the three in which at the most only slight improvement was noted, a supplementary injection of 3 and 5 mCi, respectively was given. This supplementary injection caused the effusion to disappear completely in one patient and to decrease in another The treatment produced no change in one patient with advanced arthrosis who previously had been subjected to synovectomy without any consequent improvement. (See Tables 1 and 2.)

It would appear that the desired result can often be obtained with half the activity used by MAKIN et coll. If necessary a later supplementary injection can be given and the total activity brought up to 10 mCi which is probably a suitable upper limit. We were not able to calculate the surface dose in the knee joint with any degree of accuracy because it was not possible to ascertain the size of the synovial surface which considerably varies from one patient to another It should however be stressed that the true surface dose used by MAKIN et coll. must have been much higher than that calculated

Even the use of such a small quantity of $^{198}$Au as 5 mCi will in some instances produce a marked increase in the amount of fluid in the joint the first week after the injection This swelling was so severe in three of the 21 patients that the fluid had to be re aspirated

The present authors, like MAKIN et coll feel that this method of treatment is better than external roentgen irradiation particularly regarding the distribution of the dose within the knee joint Examination for leakage to the regional lymph nodes and liver suggested that it could probably be neglected Quantitative measurements after autopsy corroborate this assumption though it must be borne in mind that the circulation may have been markedly reduced

It is felt that this method of treatment of persistent effusion of knee joints should replace external roentgen irradiation A single injection of 5 mCi $^{198}$Au is usually sufficient to produce the desired effect but should the result obtained be insufficient, a supplementary dose may be given later

## SUMMARY

Colloidal $^{198}$Au was injected intraarticularly to control an effusion of the knee joint in 10 patients with osteoarthritis and 9 patients with rheumatoid arthritis. The activity used 5 mCi, proved very satisfactory and the effusion disappeared in 13 joints and was considerably decreased in 5 joints out of a total of 21 joints of the material.

## ZUSAMMENFASSUNG

Radio-aktives Gold $^{198}$Au wurde intra-artikular zur Kontrolle von Kniegelenkergussen in 10 Patienten mit Osteoarthritis und in 9 Fallen von rheumatischer Arthritis eingespritzt. Die benutzte Ausstrahlung 5 mCi bewies sich als höchst wirksam, der Erguss verschwand von 13 Gelenken und verbesserte sich in 5 in einer Gesamtzahl von 21 Gelenken.

## RÉSUMÉ

Chez 10 malades atteints d arthrose et 9 atteints d arthrite rhumatismale, les auteurs ont fait des injections intra-articulaires de $^{198}$Au colloidal pour tarir un épanchement du genou La quantité de radioactivité utilisée, 5 mCi, a donné de bons résultats l'épanchement a disparu dans 13 articulations et a considérablement d minué dans 5 autres sur un total de 21 articulations traitées.

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# ISOTOPE TESTS OF KIDNEY FUNCTION IN PELVIC AND ABDOMINAL IRRADIATION

by

J P GREEN R BRUNEAU and P RUBIN

Pelvic and abdominal neoplasms are common causes of ureteral obstruction If such a complication is to be properly recognized and managed it is essential to know the status of the urinary tract not only prior to a course of irradiation but also during radiotherapy and the follow up period

It was felt that the isotope function test of the kidneys would be of value in following cancer patients during radiotherapy since it is effective in detecting early changes in renal function and excretion (QUINN et coll 1962) Urography is also a reliable guide for evaluating urinary tract abnormalities however in comparison with the isotope test it has the disadvantages of being time-consuming uncomfortable for the ill patient and costly when performed on a weekly or bi weekly basis

## Present investigation

In the period 1960—1962 48 patients undergoing irradiation for pelvic or abdominal malignancy were studied by repeated isotope function tests performed at varying time intervals but usually before as well as after irradiation

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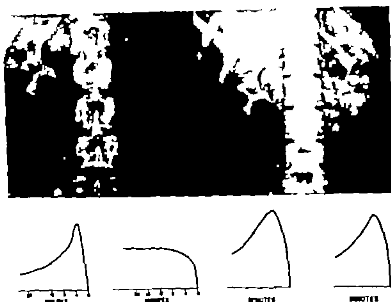


Fig 1 Stage III Hodgkin disease and involvement of left iliac nodes in 25-year old female. Left ureteral obstruction was noted at isotope test and urography at beginning of external irradiation the isotope test after 2 000 R showed normal excretion which was confirmed by urography

Of the 48 patients, 28 were examined more than twice. When urographies were available they were reviewed and correlated with the isotope test.

The material included gynecologic cancer (22 cases cervix 10, uterus 4 ovary 8) bladder carcinoma (14 cases) lymphomas (9 cases) 1 recurrent colon carcinoma, and 2 testicular tumors.

The isotope test was performed with the patient in a prone position and utilizing commercial preparations of Hippuran $^{131}$I A dose of 1 $\mu$Ci/per 6 kg

Table 1

*Isotope function test in patients (9) with lymphoma*

| | Kidney | Improved | Same | Worse |
|---|---|---|---|---|
| Non-function | 3 | 0 | 3 | — |
| Obstruction | 8 | 7 | 0 | 1 |
| Delayed excretion | 3 | 3 | 0 | 0 |
| Normal | 4 | — | 4 | 0 |
| Total | 18 | 10 | 7 | 1 |

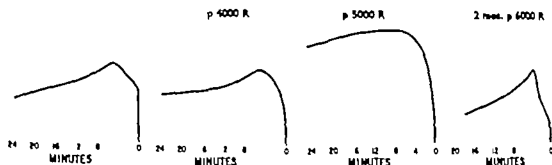



Fig 2 Isotope tests in a 56-year-old male with stage-D carcinoma of bladder; the right kidney was obstructed at the start of treatment and throughout. Isotope tests of the left kidney depict the changes that may occur on the uninvolved side solely on the basis of radiation reaction and concomitant cystitis; normal values after therapy

bodyweight was administered Each patient was hydrated with 500 ml water 15 minutes prior to injection A dual isotope detection and recording system was utilized

## Results

*Lymphomas* Among the 9 patients, 6 had lymphosarcoma 2 had Hodgkin's disease and 1 had reticulum cell sarcoma The urographic films were available for comparison in 7 cases and in each case the findings correlated well with the result of the isotope test

The ability of irradiation to reverse urinary tract obstruction caused by lymphoma is strikingly borne out by this group of patients (Table 1) Of the 9 patients, 7 had ureteral obstruction and all 7 improved either during or after irradiation (Fig 1) In some cases the response to treatment occurred relatively early and was seen with as little as 1 300 R Most of the patients responded to doses less than 2 300 R. A delayed response was seen in one patient a normal isotope function test not being obtained until 2 months after 4 000 R had been delivered to the diseased site In another patient the values returned

**Table 2**

*Isotope function in patients (14) with bladder carcinoma*

| | Kidney | Improved | Same | Worse |
|---|---|---|---|---|
| Non-function | 9 | 0 | 9 | — |
| Obstruction | 8 | 4 | 1 | 0 |
| Delayed excretion | 3 | 0 | 3 | 0 |
| Normal | 6 | | 7 | 1 |
| Total | 28 | 4 | 3 | 1 |




Fig. 3. Isotope tests and urography in 73-year-old male with stage-C carcinoma of bladder. Urography month prior to treatment showed unilateral obstruction. routine isotope tests during the first week of treatment revealed bilateral obstruction, and urography confirmed this. With progressive rise in BUN, nephrostomy was done and radiation therapy continued.

to normal 3 months after irradiation and a course of nitrogen mustard. The two patients in the lymphoma group who did not improve after radiation, both had unilateral non-function at the beginning of the irradiation therapy.

*Bladder carcinoma.* In 11 of the 14 patients with carcinoma of the bladder urograms were available and in each case the result of the isotope function test correlated well with that of urography. Twelve patients had abnormal function tests at the onset of therapy.

All patients were treated with 6 000 R in 6 weeks, except for one man who died prior to completion. A non-functioning kidney at the beginning of therapy was found to be irreversible. Of 8 obstructed kidneys, 4 were seen to improve, and 1 normal kidney showed some delayed excretion after treatment had been terminated (Table 2).

It was not unusual to see changes in the isotope function test during treatment

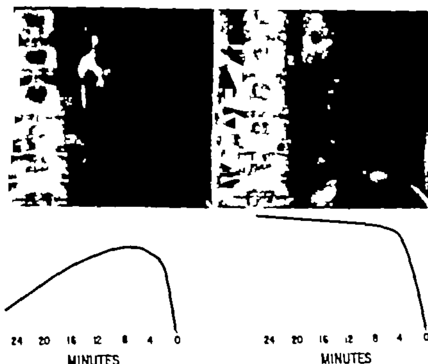



Fig 4 Isotope tests and urography in a 73-yea -old female with advanced ovarian cancer Normal left curve from isot pe test t beginn ng of treat ment two weeks later left ureteral bstruction Urography confirmed the results of the isotope test

in a kidney which was normal before and after treatment (Fig 2) Most frequently these changes consisted of slightly delayed excretion

Patients with bladder carcinoma frequently have obstruction of one kidney and it is therefore imperative to detect obstruction on the other side as early as possible These cases are particularly prone to develop an ascending pyelonephritis which is difficult to cure if the obstruction is not relieved In such patients the persistence of bilateral ureteral obstruction and the evidence of a

**Table 3**

*Isotope function test in patients (22) with gynecol gic cancer*

| | Kidneys | Improved | Same | Worse |
|---|---|---|---|---|
| Non-function | 5 | 2 | 3 | — |
| Obstruction | 6 | 2 | 3 | 1 |
| Delayed excretion | 11 | 3 | 8 | 0 |
| Normal | 22 | — | 14 | 8 |
| Total | 44 | 7 | 28 | 9 |

Table 4

*Isotope function test in patients (3) with other tumors*

| Kidney | | Improved | Same | Worse |
|---|---|---|---|---|
| Non-function | 1 | 0 | 1 | — |
| Obstruction | 1 | 0 | 1 | 0 |
| Delayed excretion | 0 | — | — | — |
| Normal | 4 | — | 4 | — |
| Total | 6 | 0 | 6 | 0 |

progressive rise in BUN should be considered indications for urinary diversion, either ureteral transplant or nephrostomy and interruption of radiation treatments until the danger period has passed (Fig 3)

*Gynecologic cancer* Among the 22 patients in this group 11 had abnormal function tests at the onset of therapy The abnormalities were evenly divided between obstruction and non function. The inability of radiotherapy to improve or reverse urinary tract obstruction in this group is in direct contrast to our experience with lymphoma. Some improvement was found in 2 of 6 kidneys, with the normal kidneys showing a tendency to develop delayed excretion at the end of or just after therapy (Table 3) The general rule here seems to be no change or progressive impairment (Fig 4)

*Other tumors* In a patient with testicular embryonal carcinoma, urography done a month prior to the beginning of retroperitoneal irradiation was completely normal A routine isotope test done after lymphadenectomy and at the beginning of radiotherapy revealed a clinically unsuspected left ureteral obstruction (thought to be a surgical complication) The finding was confirmed by urography (Table 4)

## Discussion

The isotope function test of the kidneys has been shown to be a reliable guide to individual kidney function when compared to standard renal function tests and urography (WINTER 1963) The simplicity inexpensiveness and rapidity with which it can be done make it particularly adaptable for use in observing patients undergoing pelvic and abdominal irradiation.

As a general statement, utilization of the isotope test in patients with pelvic and abdominal malignancy is indicated in the following instances.

1 As part of the base-line work up to establish the status of urinary tract drainage at the onset of radiation therapy

2 For observation of patients serially during therapy

3 In routine follow up as an indication of recurrence or continued radiation response

4 As an incentive to perform urography when the test reveals an abnormality

The isotope function test can be used as a screening procedure to detect possible ureteral obstruction in patients with palpable retroperitoneal iliac or inguinal nodes and in lymphoma patients who have the disease clinically localized above the diaphragm since a significant percentage have silent involvement of the retroperitoneal lymph nodes. With carcinoma of the bladder it is especially useful in evaluating the drainage of the upper urinary tract during irradiation since either continued tumor growth or edema in the trigone area can quickly lead to bilateral ureteral obstruction Early recognition and management of this problem can on occasion prove to be life-saving

In the lymphomas it was seen that ureteral obstruction was readily reversed probably on account of their radiosensitivity In patients with carcinoma of the bladder improvement was not so striking and patients with a non functioning kidney were not ultimately improved Patients with gynecologic cancer showed a general trend of progressive impairment or no functional improvement This is perhaps due to the more advanced and infiltrative type of lesion or it may be due to the scarring which follows tumor regression

## SUMMARY

The results of the isotope test of the kidney function in 48 patients undergoing irradiation for pelvic and abdominal neoplasms are reviewed The isotope test seems to be a reliable economical and rapid screening test.

## ZUSAMMENFASSUNG

Es werden die Resultate des Isotop-Funktionstestes bei 48 wegen Becken und abdominellen Neoplasma behandelten Patienten mitgeteilt Der Isotoptest scheint ein zuverlässlicher ökonomischer und rasch durchführbarer Test zu sein.

## RÉSUMÉ

*Les auteurs étudient les résultats de l épreuve fonctionnelle rénale par les isotopes chez 48* malades irradiés pour des néoplasmes pelviennes et abdominales. L épreuve par les isotopes paraît être un test de dépistage fidèle, économique et rapide.

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FROM THE DIVISION OF APPLIED ELECTRONICS (DIRECTOR: PROF. HENRY WALLMAN) CHALMERS UNIVERSITY OF TECHNOLOGY AND THE DEPARTMENT OF RADIOTHERAPY (DIRECTOR: PROF. MAGNUS STRANDQVIST) UNIVERSITY OF GOTHENBURG SWEDEN

# FIELD CONTROL OF TELECOBALT THERAPY BY GAMMA RAY TELEVISION

by

R. MALVÉN, B. ROSENGREN and H. WALLMAN

The usefulness of cobalt radiography in the field control of telecobalt therapy has been emphasized in an article published recently in this journal (DEBOIS & BARRY 1964). Previous reports (KUTTIG 1961 and PERRYMAN, MCALLISTER & BURWELL 1960) have stressed the importance of accurate field control in telecobalt therapy. It is the purpose of this contribution to discuss the use of gamma-ray television for this purpose, pointing out its considerable advantages over the simulator technique, conventional radiography and gamma radiography.

A fundamental characteristic of the gamma television system developed by us (Fig. 1) is that it is the therapeutic radiation that serves as source of the television image used for the control purposes.

The television equipment differs only slightly from that described in a previous publication on monitoring of radiation from a 30 megavolt betatron (BENNER, ROSENGREN, WALLMAN & NETTELAND 1962), to which reference is therefore made for technical details.

Submitted for publication 18 January 1965

2 For observation of patients serially during therapy

3 In routine follow up as an indication of recurrence or continued radiation response

4 As an incentive to perform urography when the test reveals an abnormality

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Les auteurs étudient les résultats de l épreuve fonctionnelle rénale par les isotopes chez 48 malades irradiés pour des néoplasmes pelviennes et abdominales. L épreuve par les isotopes paraît être un test de dépistage fidèle, économique et rapide.

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b

Fig. 2. Views from the television monitor during $^{60}Co$ treatment of pharyngeal carcinoma, showing epiglottis, tongue and tumour in the soft palate. The view in (b) was produced 18 days later than ( )



Fig. 3. Monitor view from the same patient as in fig. 2 and produced the same time as fig. 2b. The mandible, maxilla, and outlining of chin nd air in the nasal passages ar well rendered

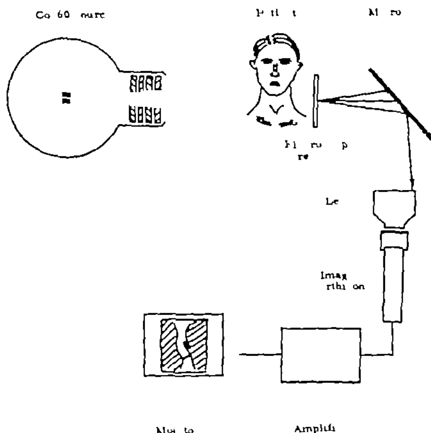



*Fig 1 The gamma television equipment shown schematically*

Television images obtained with this equipment in the treatment of *carcinoma* of the pharynx with a 5 000 curie $^{60}$Co machine (Mobaltron) are reproduced in Figs 2 and 3 The tumour is well delineated in Fig 2a, perhaps even more clearly than it would have been with conventional radiodiagnostic voltages The rapid closing of the epiglottis during swallowing is easily followed as is the passage of air to the esophagus. (A comparison of (a) and (b) in Fig 2 which were obtained at an interval of only 18 days, illustrates the response of the tumour to $^{60}$Co radiation )

The field of treatment is outlined in both the views in Fig 2 For illustrative purposes the collimators were momentarily opened to irradiate a larger field (Fig 3) The outlines of the mandible for example are depicted with considerable clarity despite the extremely small difference in absorption between bone and soft tissue of $^{60}$Co radiation A comparison of Fig 3 with photographs





b

Fig. 2. View from the television monitor during $^{60}$Co treatment of pharyngeal carcinoma, showing epiglottis, tongue and tumour in the soft palate. The view in (b) was produced 18 days later than (



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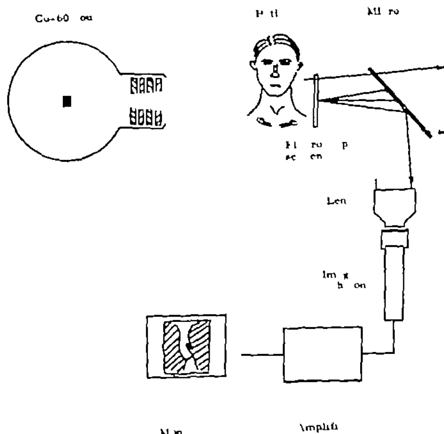



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Fig. 5 Carbon dioxide insufflated in the bladder to serve as indicator preliminary to treatment with $^{60}$Co radiation.



Fig. 6. Gold as indicator for gamma television of metastatic carcinoma of the pelvic wall. Bone structure is seen.

in calculations based on them, is similarly directly visible on the television monitor the only requirement being that the television image discloses enough anatomical detail to permit orientation Gamma television control of the field has the advantage over other methods of field control such as simulation preliminary radiography with diagnostic radiation, or with gamma radiation of complete validity There is no need to base on trust that the transfer of the patient to the therapeutic radiation will occur as planned gamma television makes it possible to see, directly and unequivocally and during every second of the treatment, whether the intended organ is irradiated.

Recognition of anatomical detail is often facilitated by the use of indicators, the best of which for $^{60}$Co are air or gas, and heavy metals such as gold and tungsten. Air is a very useful indicator and is present naturally in the pharyngeal and laryngeal region (Figs 2 to 4) Gas may also be insufflated into various body cavities, e g the bladder (Fig 5) An example of the use of gold as an indicator is given in Fig 6

## Conclusion

Although it has been contended that gammagraphy is the only possible means of direct field control in telecobalt therapy (Kuttig 1961 pp 307 and 309) such control can in fact be achieved by means of television. Gamma television not only provides better contrast than gammagraphy but has the advantage of yielding a moving picture throughout the therapeutic irradiation whatever is shown on the television monitor is, without question being irradiated at that moment by the $^{60}$Co source

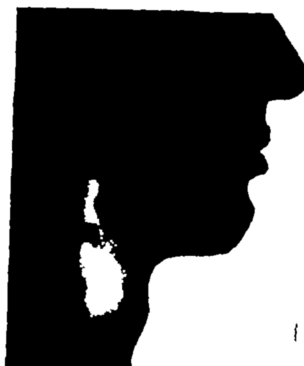


Fig 4 Treatment of carcinoma of the larynx, the submandibula gland metastases being included in the treatment field Th epiglottis, hyoid bone and air in the larynx are well shown

of the same region included in the articles on gammagraphy (e g Figs 1 to 3 in DEBOIS & BAERT Fig 7 in KUTTIG Figs 5 to 11 in PERRYMAN McALLISTER & BURWELL) shows the superior contrast obtainable with the television procedure The explanation lies in the contrast enhancement that is possible when picture information is available in electronic form by means of appropriate electronic circuitry in the television chain

The lack of sharpness that is evident in Figs 2 and 3 is the result of the large (20 mm) focus of the $^{60}$Co source this lack of sharpness applies to gamma graphy as well It is unfortunately impossible or possible only to a very limited degree to achieve sharpness enhancement by means of television circuitry

Contrast enhancement represents one advantage of gamma television over gammagraphy More important however is the fact that the gamma television image is available during the whole course of the therapeutic irradiation Any disturbance of the treatment field during the irradiation because of imperfect fixation of the body or movement of an internal organ is immediately visible on the television monitor Corrective action can then be taken at once either the irradiation is interrupted if this is deemed necessary or as is the case in one of our treatment rooms, a servo-system is actuated to return the patient to the correct position relative to the radiation source Any error in beam orientation because of an incorrect system of superficial landmarks or

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# CHOROIDO-RETINAL DAMAGE AS A COMPLICATION OF RADIOTHERAPY

by

MARJORIE PERRERS-TAYLOR, DIANA BRINKLEY and TEGWEDD REYNOLDS

During the past 14 years, those patients attending the Radiotherapeutic Centre of Addenbrooke's Hospital who have had radiotherapy near the eyes, have been kept under ophthalmological observation in addition to the usual follow-up.

It has been observed that a certain number of these patients appear to have developed characteristic changes in their choroid and retina. The changes have been observed in the patients on whom the posterior section of the eye could not be completely protected owing to the situation of the lesion undergoing treatment. A description of some of these cases follows, and also a discussion on the nature of the changes.

*Changes* All changes attributable to roentgen therapy including those of the choroid and retina that we are going to describe can be seen at times in the elderly These changes include punctate staining of the cornea, atrophy of the iris, glaucoma and cataract.

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## SUMMARY

The field control of telecobalt therapy based on a special system of gamma ray television is described Its advantages are discussed

## ZUSAMMENFASSUNG

Ein spezielles System mit Fernsehapparat für Feldkontroll bei der Telekobalt Therapie mittels Gammastrahlung wird beschrieben und die Vorteile werden besprochen

## RÉSUMÉ

Description du contrôle de champ en télécobalt-thérapie au moyen d un système spécial de télévision pour les rayons gamma, qui donne un meilleur contraste et des résultats plus surs Discussion de ses avantages.

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Fig 1 Case 1. Arterio-sclerotic retinitis.

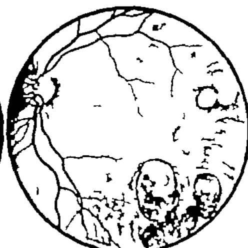


Fig 2. Case 2. Choroido-retinitis.

In all cases the choroido-retinal lesions occurred in that part of the fundus which would have received the highest dose of radiation In none of these cases was there systemic disease

## Case reports

*Case 1* Man, aged 40, with rodent ulcer along the whole length of the left eyebrow A 6.5 × 2.5 cm lead cut-out was used for the treatment with 220 kV roentgen rays. The maximum total dose to the retina was estimated to hav been not more than 000 R in 8 days. An internal ey shield as used during the treatment.

The skin reaction was excessive and telangiectases developed later Shortly after treatment there was very definite punctat staining of the left cornea, but this had cleared six months later There was alopecia of the left upper lid. The vision was 6/6.

T years after treatment, vision in the left eye became blurred and the vision dropped to 6/ 4 The fundus showed many patches of fresh fluffy exudates but no haemorrhages. Tw months later the fundus was clearing and the vision had returned to 6/9 After a further three months the left fundus showed fresh activity with many fluffy exudates and some small haemorrhages, the picture being typical of an arteriosclerotic retinitis (Fig. 1) The vision in the ey was 6/18. The fundus changes have continued slowly but steadily with drop of ision to 6/36 and at present, seven years after treatment, the changes resemble those of retinitis circinata Throughout the whole period the right fundus and vision have been normal.

*Case 2* Man, aged 46, with rodent ulcer of the left temple extending to the eyelid and down on to the cheek which was treated with 220 kV roentgen rays using an 8 × 6 cm ellipse-shaped field. A reconstruction of the treatment suggests that the retina could hav received 1 500 R to 2 000 R in 8 days. The damage sustained is described below

One year after treatment there was excessive scarring of the skin in the treated area. This patient complained of diminution of vision in the left eye after treatment. The left cornea

The majority of patients requiring deep roentgen treatment are over 40 and it is in this period of life that vascular disease and mild senile diabetes most commonly occur Fundus changes have not, therefore been attributed to radiation when the patient had a raised blood pressure or glycosuria It was, however interesting to note that in cases where there were bilateral fundus changes they were more advanced in the eye which had been exposed to roentgen therapy This was also noted in relation to senile cataract and several patients drew attention to the fact that the vision of the exposed eye since treatment had deteriorated more than the vision of the other eye It was also noticed that in all the patients who developed choroido-retinal changes, the skin reaction following roentgen therapy was unusually severe.

The fundus changes were broadly classified as follows

1 *Severe temporary choroidal pallor with small retinal vessels* probably due to constriction of vessels coming on a few weeks after a high dose of roentgen rays and slowly improving over the following months

2 Choroido-retinal atrophy with a variable amount of pigmentation at the edge This change develops about 12 months after treatment.

3 Acute choroiditis with fluffy exudate later developing pigmentary disturbance with small haemorrhages This change comes on after several months and settles slowly with periods of exacerbation over several years.

4 Retinal changes of arteriosclerotic type with small retinal haemorrhages which absorb and recur with patches of fluffy exudate and very little pigmentary disturbance These changes appear about 12 months after roentgen treatment and gradually spread over the whole fundus causing loss of central vision

5 Atrophy of the retina

After changes had been observed in a few patients who had had radiotherapy near their eyes, the records were searched to find other patients who would probably have been similarly exposed

Of 119 patients traced and examined significant changes were found in twenty four changes were present but were regarded as of doubtful significance in fourteen and in eighty-one patients there were no discernible changes.

In order to estimate the dose of ionizing radiation received by the choroid and retina in these patients who developed the changes described the treatment plans were reviewed

In two cases of carcinoma of the antrum the dose to the retina was estimated from the isodose curves. In the other cases, the treatment set up was reconstructed on a skull The cranium was filled with wax, and the surface was covered with a thin layer of wax The doses were measured with a BD 2/10 ionisation chamber placed at the back of the eye socket behind a wax eyeball of diameter 2 5 cm

*Case 4* Woman, aged 59 with carcinoma of the left antrum treated with caesium gamma ray teletherapy. T fields were used with wedge filters. The dose to the lowest part of the eye was estimated at 2 000 R to 5 000 R in 28 days. Certain fundus changes were noted shortly after treatment, but it is still too early for the later changes t have fully developed.

This patient was seen shortly after a high dose of gamma ray therapy and it was interesting to note that the whole of the left fundus was ery much paler than that of the right, and in addition, the retinal essels in the left eye were smaller than those of the right eye. The vision was 6/9 6/7 5. Three months later the pallor was still present but was less marked than on the previous examination.

Approximately a year after the treatment was given, the pallor of the right fundus was still definite, particularly below but much of the upper part had returned to an almost normal colour There was then suggestion of pigmentary disturbance in the lower part of the fundus, and the vision in the left ey had dropped to 6/24 Excessive scarring was showing on the skin of the upper cheek. Two years after treatment the lower part of the fundus showed definite choroidal atrophy with early pigmentary disturbance.

The changes in this case illustrate the development of choroidal pallor

*Case 5* Man, aged 66 with large rodent ulcer on the right side of the nose, extending on to the cheek. It was excised and recurred after 15 years, and again after a further 19 years. It as then treated with indium gamma-ray teletherapy a 6 × 5 cm ellipse-shaped field being used. The estimated total dose to the retina was approximately 1 800 R in 14 days.

There was excessive scarring of the treated skin.

Soon after the treatment, punctate staining of the right cornea was noticed but this cleared up in three months. After tw years, some radio-necrosis of the skin developed, with a return of the punctate staining, which cleared as the skin healed. There was obstruction of the canaliculus, and choroido-retinal changes were noted in the lower nasal area. These consisted of a circumscribed area of complete choroidal trophy larger than the disc with little pigmentation at the edge in places.

Early senile lens changes were noted. There were no abnormal findings in the left ey throughout the period of observation.

This patient died in 1961 at the age of 73, seven years after his treatment. The changes fall in with those grouped as choroid-retinal trophy

*Case 6* Man, aged 70 at the time of the first treatment. He had squamous cell carcinoma of the left upper eyelid, which was of an infiltrating type and extended along the whole length of the upper lid and round the outer canthus, and involved the conjunctiva and orbital margin

Treatment was given with 220 kV roentgen rays, the cornea and lens being shielded. A recurrence developed four months later on the lower lid, and further course of 220 kV roentgen rays as given.

Six months later recurrence developed at the outer canthus and a further treatment was given with much lead shielding. A year later further recurrence developed, and the eye was removed, together with some of the surrounding tissues the area was grafted. The histologic report suggested that the excision was complete.

A reconstruction of the various radiation treatments suggests that he received retinal dose of 2000 R to 3 500 R. This was received from two of the treatment courses which were given in 21 days and 8 days

Extensive keratitis was noted few days after the first treatment course was completed.

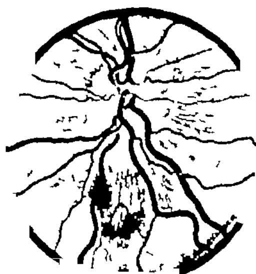


Fig 3 Case 3 Pigmentary disturbance

showed punctate staining and fresh gross choroido-retinal changes in the upper temporal area. Six months later the fundus changes were settling down and developing much pigmentation.

After four years the left cornea was still staining and there was fresh activity in the area of choroido-retinitis (see Fig 2) with further haemorrhages and exudates these were extending down towards the disc. There was much mucus on the cornea and it was thought that probably the lacrymal gland had been damaged by the treatment.

In the following year the fundus changes were still active but six to seven years after treatment the fundus appeared quieter although the cornea was still staining Eleven years after the course of roentgen ray therapy the fundus changes again became active, and these changes extended nasally towards 12 o clock and down towards the macula the cornea was still staining

Thirteen years after treatment, the fundus picture still showed active changes, and the vision in the eye had dropped to 6/12 Corneal staining continued Throughout the period of observation the right eye remained normal

*Case 3* Man, aged 57 with an advanced carcinoma of the left antrum which had destroyed all the antral walls and extended into the ethmoidal and sphenoidal sinuses. Treatment was given with 220 kV roentgen rays, two lateral and one anterior field being used. The total maximum dose to the retina was approximately 2 700 R to 3 100 R in 24 days. The changes described below have since developed

Shortly after treatment, an oval white area was seen just below the disc in the left eye and this gradually became raised and greyish There was punctate staining of the cornea which cleared after eight months the vision was 6/18 6/6 The fundus was examined periodically and after eight years, the area had not increased in size but was darker and had developed a yellow spot in the centre which cleared after a further period of a few months. There was no increase in size of the raised grey area, but there was marked scarring of the skin. Ten years later the area had become more pigmented The pigmentary disturbance is illustrated in Fig 3

There is marked oedema and haemorrhage of the limbus, with irregularity of the corneal epithelium. The corneal stroma and endothelium appear normal, while the filtration angle is patent and the lens unremarkable. Some oedema is evident in the ciliary body but the chief changes are to be seen in the retina, where there is pronounced peripheral cystic degeneration, more marked than is seen normally. The retina is atrophic, particularly in its inner layers, here the inner nuclear layer is extremely tenuous and ganglion cells are greatly reduced in number. At one end of the section the retina is detached and I suspect this is due to artefact in preparation. The visual cells are normal apart from some slight vacuolation due to post mortem change. The pigment epithelium and choroid show no significant abnormality and the sclera is normal.

## Discussion

Lens damage as a late complication of radiation has been reported by many authors (e.g. CHALUPECKY 1897, POPPE 1957, COGAN 1958, MITCHELL 1952). Choroidal burns following treatment of the eye with radon seeds or with the application of radium plaques are described by FOSTER MOORE (1935) and STALLARD (1947), but choroido-retinal damage after treatment to skin lesions near the eye does not seem to be well recognized.

Experiments have been conducted in monkeys (BROWN et coll. 1951 and CRIS & BROWN 1955); they have shown that using cobalt gamma rays, doses of 2 000 R will destroy the retinal rods. Considerably higher doses will induce morphologic changes in all retinal structures.

Changes in the choroid have been noted in the eyes of atom bomb casualties, but these are thought to be due to blood changes rather than to direct radiation damage (WILDER 1947). During the radiation treatment of lesions near the eye, great care is taken to shield the lens, but if the lesions to be treated are near the edge of the orbit, then a considerable dose of irradiation will inevitably reach the retina and choroid, as can be seen from Fig. 5.

It is appreciated that using roentgen rays of a lower kilovoltage will reduce the dose reaching the retina. We have reviewed the treatment given to three of our illustrative cases and estimated the dose that would have been received at the retina if 100 kV roentgen rays and not 230 kV roentgen rays had been used.

In these cases the dose received would have been very much lower but in order to achieve the prescribed depth dose in these patients the use of 100 kV roentgen rays would have resulted in an excessively high skin dose. In addition the areas treated were situated directly over bone.

A superficial punctate keratitis and gross constriction of the blood vessels (choroidal and retinal) appears to occur in the exposed area in the first few weeks after treatment. If this constriction is prolonged, it can well account for the choroidal atrophy, pigmentary disturbance and retinal degeneration,




Fig 4 High-power illustrations of rea of cyst degenerat n and retinal trophy (upper ew) and of rea where changes are not so severe (middle iew) Lo er power illustration of sect on through th ey is shown i the bottom view Arrows ndicate the reas used for the two high power illustrations above.

He was examined frequently during the next three months, but at the end of this period nothing def nite was found in the fundi

There was no further ophthalmic exam nat on before exenteration of the orbit two years later A section of the eye as made (F g 4 and Professor Norman Ashton very kindly examined this and reported as follo s

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In these cases the dose received would have been very much lower, but in order to achieve the prescribed depth dose in these patients the use of 100 kV roentgen rays would have resulted in an excessively high skin dose. In addition the areas treated were situated directly over bone.

A superficial punctate keratitis and gross constriction of the blood vessels (choroidal and retinal) appears to occur in the exposed area in the first few weeks after treatment. If this constriction is prolonged, it can well account for the choroidal atrophy, pigmentary disturbance and retinal degeneration,

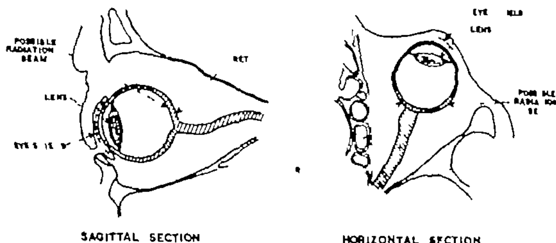



Fig 5 Schematic view of horizontal and sagittal sections thro gh th orbit to illustrate the relative positions of eye shield lens and retina

similar to but milder than a radium burn In the arterio-sclerotic type, possibly the retinal vessels are more damaged than the choroidal vessels.

Only one eye in this series had to be removed and sections showed atrophic changes in the inner retinal layers with no significant changes in the pigment layers but owing to the site of the lesion (upper lid) the eye would have received more protection than in some of the other cases

The cases described had quite high doses of irradiation the minimum being 1 000 R and the maximum 3 500 R Nerve tissue is regarded as being one of the less radiosensitive structures, but damage will occur directly at high doses ARNOLD (1954) CLEMENTINE & HOLST (1954) and spinal cord damage has been recorded after 3 500 R DUKE ELDER regards 3 000 R as the level which is safe for the retina However indirect damage to nerve cells may occur through irradiation of small blood vessels which are more sensitive than nerve cells It would seem likely that the changes seen are primarily due to blood vessel damage

In the two cases of carcinoma of the antrum described the treatment was planned while knowing that one eye would risk damage but with the rodent ulcer treatments it was thought that the use of an internal eye shield was sufficient protection In two of the rodent ulcer cases who were in their forties the damage has been severe and progressive The vision has been reduced to 1/6 in one case and one half standard vision in the other case Fortunately in both patients the unexposed eye is normal. If a patient already had defective vision treatment of this nature could cause near blindness.

It would therefore seem prudent to bear these risks in mind when planning deep roentgen therapy to these areas Patients should have both eyes examined

before starting out on such a course treatment, and if by any chance the sight in one eye is defective it would perhaps be better to advise surgical excision and if necessary plastic repair rather than risk the type of damage here described.

## Acknowledgements

We would like to acknowledge the help and encouragement which Professor Mitchell has given us in carrying out this investigation. We would also like to acknowledge the help given by the staff of the Radiotherapy Department of Addenbrooke's Hospital and in particular Mr J. L. Haybittle for his helpful criticisms. Professor Ashton kindly gave us his opinion on the section of the eye for which we would like to thank him.

## SUMMARY

A description is given of choroido-retinal changes occurring after irradiation treatments near the eye. Details are given of six cases with illustration of the fundi. When treating skin lesions in certain sites around the orbit, it seems difficult to avoid quite large doses of radiation reaching the choroid and retina when standard forms of radiotherapy are used. It appears that these doses of irradiation of the order of 1 500 R upwards are sufficient in some cases to cause permanent choroido-retinal damage, probably by initially affecting the small blood vessels.

## ZUSAMMENFASSUNG

Es wird das Auftreten von chorioido-retinalen Veränderungen nach Strahlenbehandlung in der Nähe des Auges in 6 Fällen beschrieben und diskutiert, und Abbildungen mit Details des Fundus und wiedergegeben. Bei den üblichen Formen der Strahlenbehandlung von Hautveränderungen, die an gewissen Stellen der Orbita lokalisiert sind, ist es schwierig zu vermeiden dass ziemlich grosse Strahlendosen die Chorioidea und Retina treffen. Es scheint als ob Strahlendosen von 1 500 R aufwärts in manchen Fällen für das Auftreten von permanenten chorioido-retinalen Schäden genügen, wahrscheinlich dadurch verursacht dass die kleinen Blutgefässe initial geschädigt werden.

## RÉSUMÉ

Description des lésions choroïdo-rétiniennes survenant après radiothérapie au voisinage de l'oeil. Les auteurs donnent des détails sur six cas, avec des photographies du fond d'oeil. Il semble difficile, au cours du traitement de lésions cutanées en certaines régions autour de l'orbite, d'éviter que d'assez fortes doses de rayonnement atteignent la choroïde et la rétine quand on emploie les formes habituelles de la radiothérapie. Il semble que dans certains cas des doses de l'ordre de 1 500 R suffisent pour causer une lésion choroïdo-rétinienne permanente, probablement en affectant initialement les petits vaisseaux sanguins.

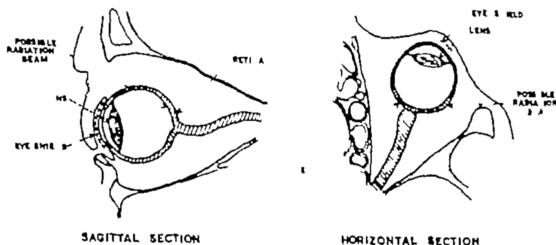



Fig 5 Schematic view of horizontal and sagittal sections through the orbit to illustrate the relative positions of eye shield, lens and retina.

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In the two cases of carcinoma of the antrum described the treatment was planned while knowing that one eye would risk damage but with the rodent ulcer treatments it was thought that the use of an internal eye shield was sufficient protection In two of the rodent ulcer cases, who were in their forties the damage has been severe and progressive The vision has been reduced to 1/6 in one case and one half standard vision in the other case Fortunately in both patients the unexposed eye is normal If a patient already had defective vision treatment of this nature could cause near blindness.

It would therefore seem prudent to bear these risks in mind when planning deep roentgen therapy to these areas Patients should have both eyes examined

FROM THE DEPARTMENT OF RADIOTHERAPY (DIRECTOR PROF M. LINDGREN)
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# RADIOLOGIC TREATMENT OF ORBITAL LYMPHOMA

by

SUNE AHLSTRÖM MARTIN LINDGREN and HANS OLIVECRONA

Lymphomas represent a comparatively small group of orbital tumours. GODTFREDSEN (1947) OFFRET (1951) and REESE (1951) found about 15 per cent of lymphomas in their respective materials of growths of the orbit. GODTFREDSEN & LINDGREN (1953) published an account of a series of 12 orbital lymphomas. Apart from LEDERMAN (1956, 1957 a and b) who reported the technique and results of radiation treatment, most authors have studied these tumours chiefly from an ophthalmologic point of view The increasing knowledge of the histology and clinical course of orbital lymphomas has resulted in a change of treatment from the earlier combined surgical-radiologic treatment to nowadays accepted radiotherapy alone.

*Material* Nine patients with orbital lymphoma, three of whom had bilateral growths were treated during the period 1946—1959 The tumours comprised seven orbital, three epibulbar one *palpebral, and one intraocular growths* they all had smooth surfaces and were of a soft, elastic consistency The anterior part was well outlined, but for anatomical reasons the position of the posterior part could not be determined exactly which is important from a radiotherapeutic standpoint.

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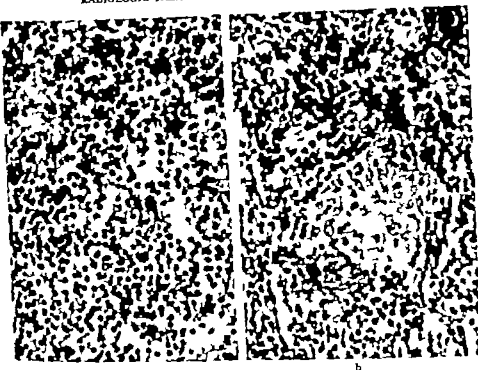


Fig. 1. Microscopic ppearance of an orbital lymphoma. ) Evenly distributed, densely packed lymphocyte-like cells. b) Development of follicle-like structure 400.

included lateral orbital field with dose of 1 500 rad over a period of 9 days. The treatment resulted in successive decrease of the growth and ultimately its complete disappearance.

*October 1949.* A small tumour of the right breast was removed and proved to have similar microscopic appearances as the lesion in the orbit interpreted as probably being a benign lymphadenoma.

*November 1964.* Patient well and free of symptoms.

*Case 4.* Male, aged 65, who had had slowly growing tumour located subconjunctivally and medially in the right eye for eighteen months.

*June 1948.* Biopsy showed the tumour to be probably benign lymphadenoma. Roentgen therapy administered against an anterior orbital field with dose of 1 000 rad over period of 5 days. One month later small rest of tumour persisted contact roentgen therapy given on one occasion in dose of 1 000 rad (50 kV 2 mm Al HVD 8 mm $H_2O$) caused its complete disappearance within three months.

*November 1954.* A tumour present in the left mammary ppeared on microscopy to be benign lymphadenoma it was treated with roentgen therapy

*December 1955.* A tumour was observed in the subconjunctiva of the left orbit no biopsy was performed. Roentgen therapy in one series against an anterior orbital field with dose of 1 300 rad over period of 9 days caused complete regression of the tumour within month.

The tumours were examined histologically in all nine instances. Biopsy was performed on one side only in the 3 patients with a bilateral growth a malignant lymphoma was revealed in 3 patients but in the remaining 6 patients the appearances were difficult to interpret The growth was composed of densely packed lymphocytes, and the formation of follicle-like structures was observed occasionally (Fig 1) BÄFVERSTEDT LUNDMARK, MOSSBERG & STENBECK (1956) have reported one instance of lymphoma of the orbit with similar histologic appearances and suggested that they were identical with those of lymphadenoma benigna cutis, described by BÄFVERSTEDT (1943)

## Case reports

*Case 1* Female aged 66 who had had a tumour in the upper medial aspect of the left orbit for six months. Biopsy revealed malignant lymphoma

*July 1957* Roentgen therapy in one series against an upper anterior and a lateral orbital field with a dose to each of 1 500 rad over a period of 11 days produced *complete regression* of the tumour by the end of the treatment

*November 1957* Enlarged lymph nodes noted in both groins and axillae, and small tumours in the skin of the left breast biopsy of the latter revealed malignant lymphoma. Roentgen therapy resulted in the disappearance of the changes.

*February and July 1963* The examination of small tumours extirpated from the right thigh disclosed malignant lymphoma.

*May 1964* Patient well and free of symptoms

*Case 2* Male, aged 61 who had had a tumour in the upper medial aspect of the right orbit for nine months proved on biopsy to be a malignant lymphoma.

*August 1957* Roentgen therapy *in one series against an upper anterior* orbital field with a dose of 2 800 rad over a period of 8 days resulted in complete disappearance of the tumour no growth present one month later Free of symptoms until December 1962 when a mass appeared in the left gluteal region.

*May 1963* Enlarged lymph nodes noted in the right inguinal region Biopsy from both locations disclosed malignant lymphoma Cavography demonstrated a right-sided pelvic tumour Roentgen therapy against both sides of the pelvis

*May 1964* Enlarged lymph nodes appeared on the right side of the neck. Biopsy revealed malignant lymphoma of the same appearances as at earlier investigations. Roentgen therapy administered.

*September 1964* Patient well and free of symptoms.

The patient died in November 1964 autopsy revealed malignant lymphoma in abdominal lymph nodes and in the liver

*Case 3* Female, aged 51 who had had *a slowly growing tumour* at the medial aspect of the base of the left orbit for sixteen months.

*September 1946* The tumour was partially removed and was considered to be either a lymphosarcoma or a benign lymphadenoma. Roentgen therapy *was given in two series* against an anterior orbital field with a dose of 2 800 rad over a period of 56 days the first series also

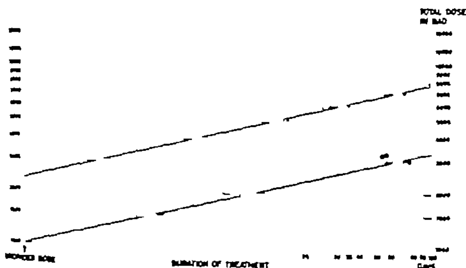



Fig. 2. Strandqvist-diagram showing the tumour dose given in 12 instances of orbital lymphoma. The upper line represents the dose needed for healing cancer of the skin the lower line shows the dose levels on different days corresponding to single dose of 1 000 rad

Biopsy could not be performed. Roentgen therapy in tw series against a lateral orbital field with total dosage of 3 200 rad over period of 45 days resulted in the disappearance of the tumour and the blatio Before treatment, the visual acuity was 0.1 and after treatment it rose temporarily to 0.3 but later fell to 0.1 because of an incipient irradiation cataract.

*February 1961* A tumour extirpated from the left arm proved to be malignant lymphoma. Roentgen therapy was given.

*July 1961* Roentgen therapy was administered to a tumour of the right cheek no biopsy

*February 1963.* A small tumour in the right breast proved on biopsy to be malignant lymphoma it was treated with roentgen therapy

*October 1964* A tumour of the upper lip proved on biopsy to be malignant lymphoma roentgen therapy caused complete regression.

*November 1964* Patient was in good general health.

*Case 9.* Male, aged 58, had had right exophthalmus for the previous six months. A tumour situated in the upper medial aspect of the orbit was considered on biopsy to be either benign lymphadenoma or lymphosarcoma. Roentgen therapy in tw series (1) against an upper and lower orbital field, as well as against a lateral orbital field, (2) against only the lateral orbital field The dose to the two anterior fields was 1 000 rad against each over period of 51 days and the dose to the lateral field in the two series was 3 000 rad over period of 56 days T months after the beginning of the treatment there was complete regression of the exophthalmos and no growth was evident in the orbit. Slight paresis of the superior oblique and the inferior rectus muscles was noted later about 2 mm degree of enophthalmus was observed.

*October 1964* Patient well and free of symptoms.

*February 1957* The patient was operated on for carcinoma of the stomach In addition to an adenocarcinoma microscopy revealed a malignant lymphoma located in the gastric mucosa and in abdominal lymph nodes.

The patient died in August 1959

*Case 5* Male aged 82 who on two occasions during the previous three years had had a temporary protrusion of the right eye, a condition that had become permanent during the previous twelve months A tumour evident in the upper part of the right orbit appeared on biopsy to be a benign lymphadenoma. Roentgen therapy against an upper anterior and a lateral orbital field with a dose to each field of 1 500 rad over a period of 10 days produced disappearance of the tumour two months later

*October 1958* A growth that no was present at the lower margin of the right orbit had the same appearances on microscopy as the previous tumour Roentgen therapy was given against an inferior anterior orbital field with a second series against the same lateral field as treated earlier each field received a dose of 1 500 rad over a period of 12 days No growth was evident two months later

*February 1959* A tumour of appearance similar to the previous growths, appeared in the right parotid region and was again treated with roentgen therapy

*April 1963* Patient well and free of symptoms.

The patient died in October 1964 from cardiosclerosis.

*Case 6* Female aged 47 with slowly increasing left exophthalmus for six months.

*February 1950* Biopsy of a left orbital tumour suggested a benign lymphadenoma. A small growth was also present in the right upper eyelid Roentgen therapy in two series was given against both orbits. On the left side two lateral fields, a lower at the level of the orbit and an upper field over the lateral frontal region were used treatment on the right side was given against an anterior and a lateral orbital field The dose in the two series to each field on the left side was 2 400 rad over a period of 75 days and on the right side 2 100 rad over a period of 63 days. A rapid decrease of the tumour mass occurred on both sides, and within five months the tumours had disappeared

*November 1964* Patient well and free of symptoms.

*Case 7* Female, aged 46, with downward displacement of the right eye for a month.

*May 1947* A growth in the upper part of the right orbit which on biopsy appeared to be a benign lymphadenoma. Roentgen therapy in two series against an upper anterior orbital field with a dose of 3 500 rad over a period of 53 days resulted in disappearance of the tumour two months later Free of symptoms until December 1957 when bilateral inguinal lymph nodes enlargement was proved to be due to malignant lymphoma. The disease rapidly progressed with several new manifestations and the patient died in July 1958.

*Case 8* Female aged 55 who had had a tumour of the soft palate for five months.

*November 1949* Biopsy suggested the presence of a malignant lymphoma Roentgen therapy resulted in complete disappearance of the signs.

*October 1954* A tumour that had appeared subconjunctivally on the upper medial aspect of the right eye, was found on microscopy to have appearances similar to those of the soft palate Roentgen therapy in two series against an anterior orbital field in a total dose of 2 000 rad over a period of 42 days caused the tumour to disappear

*September 1959* Impaired vision of the left eye was found to be du to an intraocular tumour that had caused ablatio retinae a retrobulbar tumour had produced protrusion of the eye

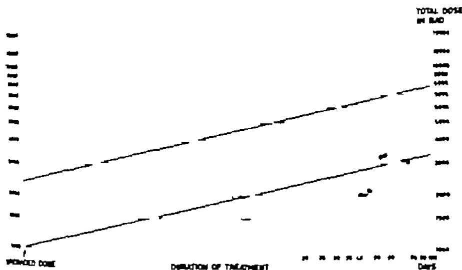



Fig. 2. Strandqvist-diagram showing the tumour dose given in 12 instances of orbital lymphoma. The upper line represents the dose needed for healing cancer of the skin; the lower line shows the dose levels on different days corresponding to a single dose of 1 000 rad.

Biopsy could not be performed. Roentgen therapy in two series against a lateral orbital field with a total dosage of 3 200 rad over a period of 45 days resulted in the disappearance of the tumour and the ablatio. Before treatment, the visual acuity was 0.1, and after treatment it rose temporarily to 0.3 but later fell to 0.1 because of an incipient irradiation cataract.

*February 1961.* A tumour extirpated from the left arm proved to be a malignant lymphoma. Roentgen therapy was given.

*July 1961.* Roentgen therapy was administered to a tumour of the right cheek, no biopsy.

*February 1963.* A small tumour in the right breast proved on biopsy to be a malignant lymphoma. It was treated with roentgen therapy.

*October 1964.* A tumour of the upper lip proved on biopsy to be a malignant lymphoma; roentgen therapy caused complete regression.

*November 1964.* Patient was in good general health.

*Case 9.* Male, aged 38, had had right exophthalmus for the previous six months. A tumour situated in the upper medial aspect of the orbit was considered on biopsy to be either a benign lymphadenoma or a lymphosarcoma. Roentgen therapy in two series: (1) against an upper and a lower orbital field, as well as against a lateral orbital field, (2) against only the lateral orbital field. The dose to the two anterior fields was 1 000 rad against each over a period of 11 days, and the dose to the lateral field in the two series was 3 000 rad over a period of 56 days. Two months after the beginning of the treatment there was complete regression of the exophthalmus and no growth was evident in the orbit. Slight paresis of the superior oblique and the inferior rectus muscles was noted. Later about 2 mm degree of enophthalmus was observed.

*October 1964.* Patient well and free of symptoms.

*Radiation technique and results of treatment* Six patients were treated with 170 kV HVL 1 mm Cu one with 150 kV HVL 0 35 mm Cu and 2 with 100 kV HVL 0 15 mm Cu FSD 40 or 50 cm. Irradiation was given against 12 tumour localizations in these 9 patients in 10 of these 12 a single anterior field was given against the orbit, and in 5 was supplemented with a lateral field The intraocular tumour which caused ablatio retinae was treated only against a lateral field One patient with a growth situated laterally in the orbit received treatment against both a lateral orbital field and a field against the outer part of the forehead

Lead protection of the cornea was employed when a field was directed against the eye. The treatment was given with daily skin doses that varied from 150 to 300 rad The tumour dose for each patient was calculated and recorded in a diagram according to STRANDQVIST (1944) it corresponded to an accumulated dose of about 1 000 rad (Fig 2)

All the neoplasms were highly radiosensitive and they completely regressed Complete disappearance of the tumour and further healing of the detachment of the retina occurred in the patient with ablatio retinae. The visual acuity of the treated eye first rose from 0 1 to 0 3 but later fell to 0 1 because of an incipient irradiation cataract. This patient was the only one with damage to the lens, the only complication encountered in the present material

## Discussion

The clinical manifestations and the different locations of the tumours in the region of the eye in the present material agree fairly well with those previously reported (MCGAVIC 1943 FORREST 1919 HEATH 1949 OFFRET 1951 REESE 1951 GODTFREDSEN & LINDGREN 1953) Three patients had bilateral growths

The diagnosis is based on the histology of the tumour and the course of the condition It is often impossible to refer the neoplasm conclusively to a certain type within the lymphoma group The degree of malignancy in many instances cannot be determined histologically and the clinical course provides an indication of any malignant transformation of the disease A fairly strong tendency for the pathologic process to spread with the appearance of new localizations was evident in the present material thus signs appeared later of metastatic growths in seven patients with a primary lesion in the orbit It therefore seems that even though the primary tumour in the orbit does not definitely present evidence of malignant changes on microscopy the condition has a considerable tendency to degenerate into a malignant form with generalization

The neoplasms belong to the lymphoma group and can be expected to show a high degree of radiosensitivity because of this and the tendency for distant

spread, radiotherapy is to be preferred to surgery. All the orbital tumours in the present material were highly radiosensitive and disappeared completely; no local recurrence was evident. If the situation of the tumour allows protection of the cornea and lens, no damage to the eye occurs.

Because of the possibility of a malignant spread, patients with orbital lymphomas, which histologically need show no malignant characteristics, should be continuously controlled in the same manner as those with malignant growths.


## SUMMARY

Orbital lymphoma in 9 patients treated with roentgen irradiation is described. Most of the tumours presented atypical appearances and the disease followed a varying clinical course with a tendency to malignancy with distant spread. All the tumours were highly radiosensitive and disappeared completely after an accumulated tumour dose of about 1 000 rad.

## ZUSAMMENFASSUNG

Neun Fälle von Lymphom der Orbita wurden mit Röntgentherapie behandelt. Die meisten Tumoren erwiesen sich als atypisch und zeigten einen wechselnden klinischen Verlauf mit Tendenz zur Malignität und Neigung zu entfernten Metastasen. Alle Tumoren waren höchst strahlenempfindlich und verschwanden vollständig nach einer Totaldosis von ungefähr 1000 rad.

## RÉSUMÉ

Présentation de 9 cas de lymphome orbitaire traités par roentgen thérapie. La plupart de ces tumeurs avaient des aspects atypiques et ont eu une évolution clinique variable, avec une tendance à la malignité et à la dissémination à distance. Toutes ces tumeurs ont été très radiosensibles et ont disparu complètement après une dose tumeur totale d'environ 1 000 rad.


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FROM RADIUMHEMMET (DIRECTOR S. HULTBERG) THE ROENTGENDIAGNOSTIC DEPARTMENT (ACTING DIRECTOR N EDLING) AND THE DEPARTMENT OF UROLOGY (DIRECTOR G GIERTZ) KAROLINSKA SJUKHUSET STOCKHOLM, SWEDEN

# VESICO URETERIC REFLUX IN CONNECTION WITH SUPERVOLTAGE THERAPY FOR BLADDER CARCINOMA

by

FOLKE EDSMYR and ARNE E. NILSON

Cobalt 60 teletherapy was introduced at Radiumhemmet in 1957 for the treatment of carcinoma of the bladder and from 1st of July that year until 31st of May 1964 external cobalt 60 irradiation was the main form of treatment for 272 patients. It was undertaken in close collaboration between the department of radiotherapy at Radiumhemmet, and the departments of urology diagnostic radiology radiopathology and clinical radiophysics at Karolinska Sjukhuset. Surgery had earlier usually been employed sometimes with implantation of radium needles, or with postoperative conventional roentgen therapy The results were however not satisfactory until the introduction of supervoltage treatment which produced a striking improvement (EDSMYR, JACOBSSON, DAHL & WALSTAM 1964)

A new method of treatment is usually connected with many interesting problems including those of importance in its development. In this paper the effect of supervoltage therapy upon the vesico-ureteric area has been selected for consideration

Vesico-ureteric reflux is a serious complication because changes in the hydro-

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static conditions may eventually impair the renal function and retrograde spread of infection from the bladder may give rise to pyelonephritis, with further functional deterioration Reflux in connection with tumours of the bladder may moreover result in retrograde implantation metastases in the upper urinary tract with consequent worsening of the prognosis (NILSON 1959) The reflux in NILSON's material (1959) was attributed to damage to the ureteric orifice during surgery which in one instance was combined with conventional roentgen therapy and in another with implantation of radium needles

Since intravesical irradiation with radioactive isotopes often gives rise to secondary changes in the bladder wall and to reflux (EINHORN HULTBERG & NILSON 1964) it was considered important to determine whether external irradiation with cobalt 60 could likewise impair the valvular function of the ureteric orifice. A preliminary report on the treatment of 43 patients was published by EDSMYR & NILSON (1964) This study which was begun in November 1963 was related to new patients who had not received radiotherapy as well as to those who had been admitted for the usual follow-up examinations after radiotherapy for urinary carcinoma

*Method* The reflux examination was performed as miction cystography (EDLING 1945) with roll films, one exposure being made every three seconds throughout the act of micturition *Urografin 17 %* combined with *Periodal* Viscous 35 % was used as contrast medium The urography was performed in connection with reflux studies to examine flow and anatomy of the upper urinary tract.

*Material* The series consisted of 76 patients 54 being men and 22 women with ages ranging from 38 to 81 with a mean of 64 years All the patients had undergone one or more operations, the least extensive of which was a transurethral biopsy excision in connection with cystoscopy The location of the tumour in the bladder was based on endoscopic examination The distribution according to clinical stages (IUAC 1963) was in stage T 2 29 patients stage T 3 41 patients stage T 4 6 patients.

The calculated mean tumour doses were generally 6 000 to 7 000 rad in 5 to 7 weeks (EDSMYR JACOBSSON DAHL & WALSTAM 1964) An individual irradiation program was drawn up for each patient *based on the anatomical* outlines in a section through the centre of the region to be treated The object was to provide a uniform dose over the tumour area while keeping the extrinsic irradiation level as low as possible The tumour area includes the whole of the bladder and a margin that should take account of tumour spread A colour system was applied to facilitate comparison between isodose

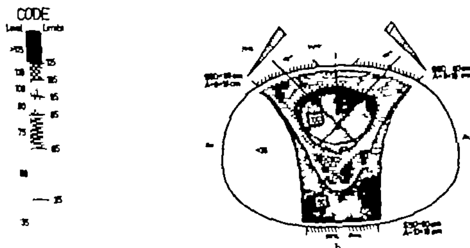



Fig 1 ) Code of patterns used for demonstrating the isodose diagrams. b) Typical dose distribution obtained with two anterior wedge fields and direct posterior field.

diagrams for different techniques the colours used in practice are represented in the diagrams by differently patterned areas (see Fig 1) The dose for the two ureteric orifices should be equal and uniform.

Satisfactory management of the treatment demands that there should be no infection when the treatment is begun this was usually ensured by intensive antibiotic therapy Bacteriologic culture and resistance tests were carried out weekly during the radiotherapic treatment and were continued at regular intervals when it had been completed. Antibiotic therapy was continued during the period of radiotherapeutic treatment and for 2 to 3 months following it. The subsequent follow up checks included complete bacteriologic and clinical examinations.

Fifteen patients were examined for reflux just before and after radiotherapy the remaining 61 being examined only afterwards. In 16 patients, the reflux test was performed immediately after radiotherapy The times elapsing between radiotherapy and the reflux test in the other patients were

| Months | Patients |
|---|---|
| 2—3 | 15 |
| 6—7 | 11 |
| 8—10 | 6 |
| 12—18 | 7 |
| 18—24 | 6 |
| 24—30 | 5 |
| 30—36 | 5 |
| 36—84 | 5 |

## Results

### *A Reflux examinations before and after radiotherapy*

In the examinations before radiotherapy reflux was observed in four out of the 15 patients examined The tumour in these four patients had involved the insufficient ureteric orifice and had occasioned one or more surgical operations In one patient, tantalum needles had been implanted adjacent to the orifice when the tumour was removed In eight of the eleven patients in whom no reflux was observed the orifices were free of tumour growth, in three others there was tumour growth in the orifice in two of these there was total obstruction and arrest of renal function and in the third the ureter had been reimplanted in the bladder at the resection of the tumour

At the repeated examinations for reflux conducted 0 to 3 months after the radiotherapeutic treatment had been completed the conditions were unchanged in all the 15 patients who had also been examined before radiotherapy was begun

### *B Reflux examinations after radiotherapy only*

Reflux was recorded in 21 out of the 61 patients examined In 18 of these the ureteric orifice was involved by tumour for which one or more operations had been performed (Fig 2) in two patients accompanied by reimplantation of the ureter on the same side The conditions were as follows in the other three patients resection of the tumour and reimplantation were performed contralaterally in one patient in the second patient there was no tumour growth in the actual orifice but in the adjacent tissues of the bladder wall in the third patient the tumour was some distance from the orifice

Tumour growth was present in the orifice in seven of the 40 patients in whom no reflux was found and in all of them it had given rise to obstruction six of these being severe enough to silence the kidney In the remaining 33 patients the tumour was distinctly separated from the orifices

*Urographic examination of upper urinary tract* Urographic checks carried out in association with the reflux examinations after radiotherapy revealed dilatation of the upper urinary tract on the side of the reflux in three out of the 25 patients The dilatation was in two of these completely or partly ascribed to obstruction to flow tumour relapse or sclerosis of the bladder wall In the third patient the dilatation could not be attributed to stenosis of a corresponding kind No dilatation of the upper urinary tract was evident in the other 22 patients with reflux.

Implantation metastases in reflux were never disclosed by the urographic method



Fig. 2. Carcinoma of the bladder in a woman of 71. *Left:* Urography disclosed tumour growth in the right ureteric orifice giving rise to partial obstruction with dilatation of the upper urinary tract. *Upper right:* Micturition cystography one year after removal of a biopsy specimen of the tumour and 10 months following radiotherapy: right vesico-ureteric reflux. *Lower right:* Urography 9 months after the reflux examination. Both ureters were of normal width.

## Discussion

Reflux was found in a large proportion of the ureteric orifices involved by tumour growth: in those in which no reflux was observed either obstruction of a ureter was present or reimplantation had been performed.

Tumour infiltration in and around a ureteric orifice may itself cause reflux by interfering with the valvular function (CAULK 1935, FRANKSON 1950). Moreover infiltrative bladder tumours are surrounded by a reaction of inflammatory cell infiltration, with oedema and fibrosis, which reduces the plasticity of the bladder wall (NILSON 1959). Surgical operation near an orifice may lead to

reflux as a sequela (NILSON 1959) A combination of these causal factors may have occurred in the present material Thus valvular dysfunction would probably be due to a reduction in tissue elasticity which itself would be a result of the above morphologic changes, the fibrosis probably being a major factor

It must be borne in mind in seeking the cause of reflux in patients who had undergone radiotherapy that examinations performed prior to radiotherapy revealed reflux at all the orifices that were involved by tumour growth but which were not completely obstructed This may indicate that the development of reflux was not due primarily to the effects of irradiation

The frequency of reflux was low i e in 3 out of 44 patients in the orifices with no tumour growth In one of these an extensive resection had been performed around the contralateral orifice with reimplantation of the corresponding ureter It cannot be ruled out that changes in the anatomy of the bladder fundus resulting from the operation had been responsible for reflux on the opposite side. The tumour had almost reached both orifices in another patient in whom there was bilateral reflux, possibly due to peritumoural reaction on the orifices Radiotherapy may however have been in some measure responsible through its effect on tissue that had already undergone alteration In the third patient the reflux cannot be explained in this way but the possibility of sequelae following a previous disease cannot be eliminated

It may therefore be concluded that supervoltage therapy in the doses mentioned usually produces no reflux in healthy tumour free and surgically undisturbed ureteric orifices When supervoltage treatment for carcinoma of the bladder is being contemplated the high frequency of reflux in the orifices involved by tumour growth should be borne in mind In certain instances, follow up reflux examinations may be indicated

It is remarkable that the upper urinary tract was normal and the renal function good in reflux with no interference with flow Since the present material would suggest that a reflux can appear at an early stage more severe involvement of the upper urinary tract might be expected with long observation periods, counted from the onset of the tumour The absence of infection is probably an important factor

Implantation metastases were never observed in the upper urinary tract in any instances of reflux This may have its explanation in the absence of conditions such as infections and dilatation that would promote implantation (NILSON 1959) Reflux should always be followed carefully by means of urography to check the renal function and the width of the urinary tract and to look for evidence of implantation metastases This is particularly important in recurrence of urinary bladder carcinoma

## Conclusions

Supervoltage therapy for bladder carcinoma in doses of 6 000 to 7 000 rad given over 5 to 7 weeks appears not to impair previously sound ureteric orifices so as to lead to reflux. On the other hand orifices involved by tumours are often insufficient and supervoltage treatment cannot therefore be considered the primary cause of reflux.

An examination for reflux is indicated irrespective of the method of treatment in carcinoma of the bladder. The presence of reflux will then demand a urographic check of the upper urinary tract, with special reference to its function and width and the possible presence of implantation metastases.

## SUMMARY

An investigation of the occurrence of reflux following cobalt 60 therapy for vesical carcinoma, in material of 76 patients, is reported. Reflux was evident in large proportion of the ureteric orifices involved by the tumour but in few of the others. Dilatation of the upper urinary tract was present in only 3 of the 25 patients with reflux. No implantation metastases ere discovered in the upper urinary tract.

## ZUSAMMENFASSUNG

Das Vorkommen von Rückfluss nach Kobaltbestrahlung von Blasenkarzinom wurde in 76 Fällen untersucht. Wenn die Uretermündungen vom Tumor infiltriert waren wurde Rückfluss in den meisten Fällen beobachtet, sonst kam Rückfluss selten or. Nur 3 Fälle von den 25 Fällen mit Rückfluss zeigten eine Erweiterung der oberen Harnwege. Implantationsmetastasen der oberen Harnwege wurden nicht beobachtet.

## RÉSUMÉ

Les auteurs ont recherché le reflux urétéral chez 76 malades après traitement par le cobalt 60 pour cancer de la vessie. Il y vait un reflux évident dans une grande proportion des cas où l'orifice urétéral était atteint par la tumeur mais seulement dans un petit nombre des autres cas. Il y avait de dilatation des voies urinaires supérieures que chez 3 des 25 malades yant un reflux. On pas constaté de greffe métastatique dans les voies urinaires supérieures.

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FROM THE DEPARTMENTS OF RADIOTHERAPY (DIRECTOR M. LINDGREN) AND
RADIATION PHYSICS (DIRECTOR K. LIDÉN), UNIVERSITY OF LUND, SWEDEN

# RECORD FORM FOR EXTERNAL BEAM THERAPY DESIGNED SPECIALLY FOR $^{60}Co$ TREATMENT WITH STATIONARY FIELDS

by

MARTIN LINDGREN and ULLA BRITA NORDBERG

The data in the records of a department of radiotherapy often lack details of treatment, which makes it difficult to assess the dose delivered to a given tumour or organ, and limits the subsequent value of the records. The introduction of high-energy irradiation has resulted in the use of more detailed records but so far no unanimity has been achieved as to what entries are necessary for the actual treatment and what entries should be made for the benefit of future research.

HERRICK discussed this problem as early as 1929 and the Standardization Committee of the Radiological Society of North America in 1937 recommended a type of record which was revised in 1960 (SCHULZ & HALE). NEWELL (1941) published a record form for roentgen therapy and the National Bureau of Standards, in Handbook 87 (1963), gives recommendations in chapter VIII.

In 1959, when treatment with high-energy radiation was started at our

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Fig 1 Pages 2 and 3 of the record form.

department of radiotherapy a record form was devised that was intended to satisfy not only the requirements of the clinician of today but also the desires of any future research worker It seemed to be advisable to include too much rather than too little in order not to miss any details of possible future use The result was that the form was so large that it had to be folded to reduce it to reasonable size (about 20 cm by 30 cm) Unlike the form recommended by the Radiological Society of North America in which all data, i e radiation and clinical data are entered in a single form this folded form is reserved for information on radiotherapy all other data is entered in the patient s ordinary hospital record sheets

The design of a record form should be such as to allow systematic entry of details of any type of radiation therapy This new form which has been in use for more than 3 years, is furnished with details on external cobalt radiation with stationary fields. The inside of the folder is mainly reserved for records of the daily treatment and data used in this routine The front page is intended for a summary of the treatment and the last page for special checks, apparatus data and fractionation diagram

Fig. 2 Page 1 of the record form.

The form has recently been somewhat revised, and is now described below

The inside of the form (page 2) has 4 identical parts, each enabling entry of data on the irradiation of a field at as many as 30 sessions (Fig 1) All technical and practical data necessary to arrange the treatment, e.g the use of a wedge filter or trimmer and the position of the patient's arms, are noted to the left. Some data are of course determined by the type of apparatus used. The page also includes sketches of all entry portals and exact notes on the centre of each field This is valuable in the event of a second treatment of the same portal, or of treatment of neighbouring regions. The approximate maximum and minimum dose received by the tumour from a single field is noted to facilitate determination of the daily dose. The actual data noted are of a conventional type i.e date, time, dose prescribed and dose measured. The page also contains three columns for exit dose and other measurements that might be of interest. Changes in the position of the portal, etc, can be noted in the column marked notes

Conventional data on the patient, such as the diagnosis, histologic information, signatures of the physician and the physicist, are entered on the front page of the folder (Fig 2) All irradiations at our department are planned

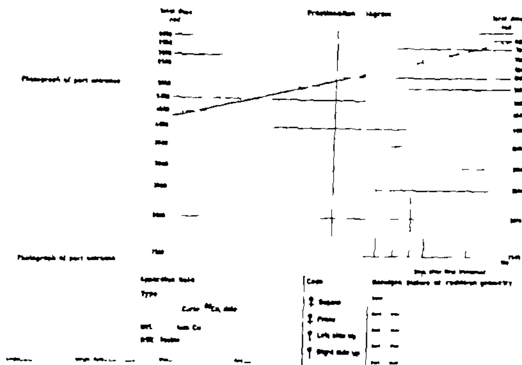


Fig 3 Page 4 of the record form

jointly by the physician and the physicist each being responsible for that part of the treatment falling within his speciality This page also contains room for information on previous radiotherapy Data on the region of the tumour are recorded to the right of this page the planned tumour dose and fractionation time, and the calculated maximum and minimum tumour dose as a percentage of the highest entrance dose It seems useful to measure the exit dose on every patient and when possible, the actual tumour dose by application of measuring chambers in the tumour or in nearby cavities of the body When the tumour dose is measured directly notes are made of the mean value and the corresponding correction if any of the calculated dose Correction of calculated dose can also be made by using the results of exit or transit measurements There is room in the form for noting the conversion factor rad/R and for the final total dose given noted as maximum and minimum dose or as modal dose mean dose, integral dose etc (Ellis 1961)

In the irradiation of tumours, the adjacent tissues may be of considerable importance according to their radiosensitivity Information on the irradiation of such tissues can also be noted calculated measured and final total dose as well as fractionation of the dose Tissues and organs of such interest are the medulla, right kidney when left kidney is irradiated the eyes, the oesoph

Fig 4 Isodose diagram for treatment of right-sided bronchial carcinoma. Transverse section through thorax line of Th 4 Outlines of tumour as well as of skeleton lungs, oesophagus and trachea are inserted.

agus if close to the irradiated region, as well as any hot spot area outside the actual region of the tumour

The number of days, the number of full turns and the tumour dose are entered on the left half of the front page (page 1) as treatment progresses. Both maximum and minimum doses in rad can be followed during the treatment. Any reaction to irradiation are noted in the column for notes.

The last page of the folder (Fig. 3) may be regarded as a continuation of page 1 It has a fractionation diagram (STRANDQVIST 1944) upon which the cumulated dose can be followed whether it is recorded as maximum and minimum dose modal dose or integral dose of the target volume. This page also contains photographs of the entry portals drawn on the patient. There is also room for the recording of roentgenograms of radiation geometry and for noting the patient's height, and the patient's weight, before, during and at the end of the treatment.

Every therapy record form is supplemented by one or more diagrams (Fig 4) upon which the region treated (tumour) anatomical details and isodose curves are inserted The design of the treatment and the dose distri

bution in transverse sections of different tissue components may be seen at a glance from such diagrams.

Record forms of the type described with supplementary dose diagrams provide a complete picture of any individual radiation treatment.

## SUMMARY

A record form for external cobalt 60 irradiation is described in detail. The form together with supplementary cross-section diagrams of the target volume allows a complete description of technical data, treatment planning and dose distribution within the irradiated region.

## ZUSAMMENFASSUNG

Eine Form von externer Behandlung mit Kobalt 60 wird im Einzelnen beschrieben. Die Art des Vorgehens zusammen mit Querschnittshilfsdiagrammen des Austrittsvolumens erlaubt die vollständige Rekonstruktion der technischen Daten, des Bestrahlungsplanes und der Dosenverteilung in der bestrahlten Region.

## RÉSUMÉ

Présentation détaillée d'une fiche de traitement pour la cobalt-60-thérapie externe. Cette fiche, accompagnée de schémas de coupes du volume-cible, permet une description complète des facteurs techniques, du plan de traitement et de la distribution de dose dans la région irradiée.

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# INFLUENCE OF TOTAL DOSE AND OF AGE ON EFFECTS OF PROTON IRRADIATION OF SPINAL CORDS OF YOUNG RATS

by

SHIRLEY ANN GILMORE

The central nervous system responds to ionizing radiation in a manner which varies with respect to the age or the developmental stage of the organism at the time of irradiation. The prenatal nervous system can be severely damaged by rather small amounts of ionizing radiation. The adult nervous system, on the other hand can withstand larger quantities of radiation but is not totally resistant to such insults. Within this range of markedly different degrees of radiosusceptibility lies the neonatal or young nervous system which has not been investigated as thoroughly.

As early as 1902 SHOLTZ showed that hindlimb paralysis occurred after irradiating the nervous system of young rabbits, and in 1906 FÖRTERLING advised the use of caution in exposing children to ionizing radiation. In spite of the early beginning of this field of investigation little detailed information is available because few studies reporting all information necessary for evaluating results have appeared in the literature. The only recent, systematic work concerned with the effects of different amounts of radiation administered to

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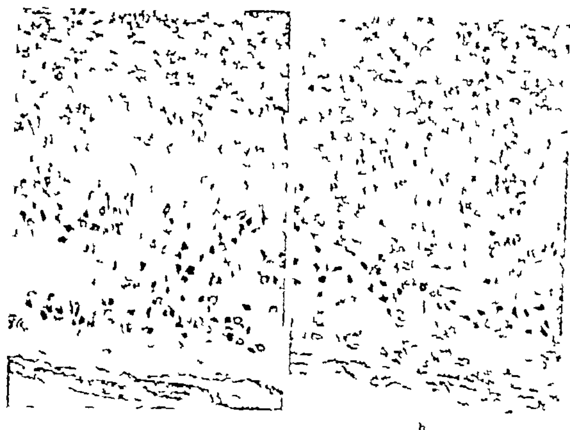
Table

*Summary of results obtained after proton irradiation of the lumbar spinal cords of neonatal rats — (1) Transient period (ca. one week) of slight neurologic changes*

| Total amount of radiation krad | Dose in rad/min | Animals in group | Age at time of irrad. day | Animals with neurol. changes | Onset of neurol. changes at days postirrad. | Animals remaining normal | Animals dead prior to neurol. changes | Animals dead after neurol. changes | Time of autopsy at day post irrad. |
|---|---|---|---|---|---|---|---|---|---|
| 12 | 1 536 | 10 | 4 | 7 | 9—10 | 1 | 2 | — | 13 or 25 |
| 12 | 1 581 | 4 | 9 | 4 | 15 | — | — | — | 23 |
| 12 | 1 308 | 8 | 14 | 4 | 22—31 | — | 4 | 2 | 34 |
| 6 | 892 | 8 | 5 | 7 | 11—12 | 1 | — | 2 | 22 |
| 6 | 683 | 8 | 11 | 4 | 23—24 | 3 | 1 | — | 39 or 70 |
| 6 | 633 | 8 | 14—15 | 1 | 47 | 7 | — | — | 63 |
| 3 | 1 363 | 8 | 4—5 | 8 | 10—12 | — | — | 1 | 18 |
| 3 | 1 023 | 8 | 11 | – | — | 8 | — | — | 63 |
| 3 | 933 | 8 | 14 | (1) | — | 8 | — | — | 70 |
| 1.5 | 2 602 | 8 | 4—5 | — | — | 8 | — | — | 69 or 70 |
| 1.5 | 1 456 | 8 | 9 | — | — | 8 | — | — | 70 |
| 1.5 | 3 418 | 8 | 14—15 | — | — | 8 | — | — | 69 or 70 |
| 0.75 | 1 681 | 12 | 4—5 | — | — | 12 | — | — | 69 or 70 |
| 0.75 | 405 | 12 | 9—11 | — | — | 12 | — | — | 70 |
| 0.75 | 985 | 12 | 14—15 | — | — | 12 | — | — | 69 or 70 |

*Material and Methods.* Adult albino rats (Sprague-Dawley) were mated and the progeny were used in this experiment. The litter size was reduced to 6 soon after birth, with each litter containing both males and females, irradiated and control. During the irradiation procedure each rat was anesthetized (45 mg/kg nembutal, intraperitoneally) and placed on its back in a lucite box constructed with an aperture in the sides of the box at the site where the proton beam passed through the spinal cord.

The 185 MeV proton beam from the synchrocyclotron at the Gustaf Werner Institute, University of Uppsala was used in this investigation. Detailed information about the physical characteristics of this beam has been published previously (LARSSON et coll. 1959, LARSSON 1961). The beam measuring 5 mm cephalocaudally by 3 mm dorsoventrally was directed through the spinal cord. The position of the animal relative to the beam was ascertained by examination of roentgenograms superimposed on an autoradiogram of the beam. In order to determine whether or not the rat had moved during the irradiation procedure, roentgenograms were also obtained after irradiation. In no case did movement occu




F g 1 ) I umba spinal cord of rat rradiated w th 12 krad when 4 day ld nd k lled 13 days later Decrease in number of neuroglia being especially evident n the whit matter Abunda t ppa ently normal neurons. b) Normal region bove th irradiated rea of spinal cord show ( ) Cresyl echt violet stain 90

different age groups is that of YAMAZAKI et coll (1960) who studied the responses of rats receiving 125 R to 1 000 R of roentgen rays to the head when 8 hours to 15 days of age This investigation showed that the majority of rats receiving 300 R or more when less than five days of age developed abnormal neurologic signs as compared with only 15 % of rats irradiated after five days of age Microscopic examination of the brains from these same animals (CLEMENTE et coll 1960) showed a correlation between the incidence of neurologic abnormalities and the neuropathology

The present investigation is one of a series of studies of microscopically noted changes and neurologic abnormalities resulting from irradiation of the spinal cords of neonatal and young rats (GILMORE 1963a 1963b 1964) Its purpose is to determine both neurologic and neuropathologic changes resulting from the administration of different amounts of high energy protons to spinal cords of rats from 3 to 16 days of age

from the remaining portions of the vertebrae. The spinal cords were embedded in paraffin, and serial longitudinal sections were cut at 10 μ and stained according to the following procedures gallocyanin hematoxylin and van Gieson, hematoxylin and eosin cresyl echt violet Mahon s method for myelin, and Palmgren s method for axis cylinders.

## Results

The data presented below are summarized in the Table The most common neurologic abnormality was bilateral flaccid paralysis of the hindlimbs, and, since this and other types of neurologic deficits in the hindlimbs have been described in detail in two previous publications (GILMORE 1963a, 1964) they will not be repeated here

*12 krad.* Seven of the ten animals irradiated at 4 days of age had neurologic abnormalities that were first noted at 9 to 10 days following irradiation. Two rats died before the appearance of any neurologic alterations, i. e before 9 to 10 days following irradiation and one remained normal throughout the experimental period None of the animals with impairment of the hindlimb function had incontinence of urine

Two of the rats were autopsied at 13 days post-irradiation, and the remaining six on the 23rd day following irradiation. Microscopic examination of spinal cords from animals killed at 13 days following irradiation revealed an obvious decrease in the number of neuroglia throughout the irradiated area (cf. Fig. 1) This same area was almost devoid of myelin (Fig 2a) whereas non irradiated areas were well-myelinated (Fig 2b) Neurons were abundant in the irradiated region and only a few were undergoing chromatolysis. Hemorrhages were noted in both the gray and white matter (Fig 2a) and vessels in the zone between irradiated and non-irradiated areas were dilated and congested The histologic changes seemed to progress from those just described to necrotic foci filled with gitter cells and debris in the spinal cords of those animals that were killed 23 days following irradiation (Fig 3) In addition to the vascular changes described above, polymorphonuclear leucocytes were abundant in the vessels. Irradiated areas that were not necrotic had fewer neuroglia than did normal non- rradiated areas. The neurons, of course were destroyed in the areas of necrosis, and some of those remaining in the adjacent areas were undergoing chromatolysis. Myelin alterations were similar in distribution to those already described, and axis cylinders were destroyed in necrotic areas. In addition to the changes noted microscopically gross examination showed that the diameter of the irradiated areas was less than that of the non-irradiated portions.

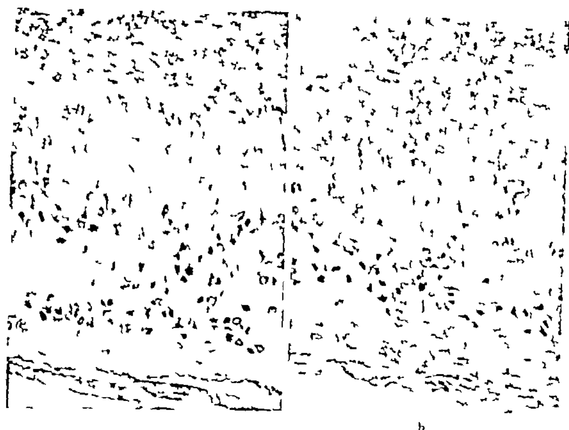



Fig 1 a) Lumba spinal co d of rat irradiated w th 12 krad when 4 day old nd k lled 13 day later Decrease in number of neuroglia being especially evident in the wh t matter Abu dant appa ently normal neurons. b) Normal region bov the irradiated rea of spinal cord show in ( ) Cresyl echt iolet t in × 90

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| 0.75 | 1 661 | 12 | 4—5 | — | — | 12 | — | — | 69 or 70 |
| 0.75 | 405 | 12 | 9—11 | — | — | 12 | — | — | 70 |
| 0.75 | 985 | 12 | 14—15 | — | — | 12 | — | — | 69 or 70 |

*Material and Methods.* Adult albino rats (Sprague Dawley) were mated and the progeny were used in this experiment. The litter size was reduced to 6 soon after birth with each litter containing both males and females, irradiated and control. During the irradiation procedure each rat was anesthetized (43 mg/kg nembutal, intraperitoneally) and placed on its back in a lucite box constructed with an aperture in the sides of the box at the site where the proton beam passed through the spinal cord.

The 185 MeV proton beam from the synchrocyclotron at the Gustaf Werner Institute, University of Uppsala was used in this investigation. Detailed information about the physical characteristics of this beam has been published previously (LARSSON et coll. 1959, LARSSON 1961). The beam measuring 5 mm cephalocaudally by 3 mm dorsoventrally was directed through the spinal cord. The position of the animal relative to the beam was ascertained by examination of roentgenograms superimposed on an autoradiogram of the beam. In order to determine whether or not the rat had moved during the irradiation procedure, roentgenograms were also obtained after irradiation. In no case did movement occu




Fig 2 a) Myelin preparation of irradiated region of spinal cord from rat receiving 12 krad when 4 days old and killed 13 days later Very little stainable myelin in white matter the blackened areas scattered throughout the section are hemorrhages. b) Normally staining myelin above the lesion shown in (a) The non-irradiated white matter is well-myelinated at this age (17) days. Mahon stain. 90

The litters were divided into the following age groups 3 to 5 days, 9 to 11 days and 14 to 16 days of age. A single dose of radiation at each of 5 levels (0 75 1 5 3 0 6 0 and 12 0 krad) was given to litters of animals in each age group The dose-rate varied within the range of 0 4 to 3 5 krad/min (cf Table) the number of rats in each group at each dose level is shown in the Table. Following irradiation the animals were examined for neurologic changes for periods up to 70 days post irradiation the length of the observation period was dependent upon the general condition of the animal and those appearing to be moribund were killed immediately

All animals were killed by decapitation A portion of the vertebral column containing both irradiated and adjacent non irradiated areas of spinal cord was rapidly excised After laminectomy the tissues were immersed in 10 % neutral formal saline for at least three days after which the spinal cords were dissected

lial cells were obviously swollen and their nuclei formed prominent bulges into the vascular lumina. The number of cells in non-necrotic, irradiated regions was increased due to a proliferation of glial cells. Nuclei of astrocytes were enlarged and irregularly shaped, and contained discrete, darkly stained basophilic rods.

Four of the 8 rats irradiated when 14 days old died within two weeks following irradiation; none had developed neurologic alterations during that period. The other four animals developed neurologic abnormalities which became evident in one rat at 22 days post-irradiation and in the other three at 29 to 31 days following irradiation. Two of these rats died several days after the onset of neurologic changes and the remaining animals had to be killed at 34 days following irradiation because of their moribund condition.

The microscopic changes in spinal cords from these animals were essentially the same as those already described for animals irradiated when 9 days old. One alteration already described, but much more pronounced in these animals, was hypertrophy and hyperplasia of neuroglia; aggregations of microglia or microglial stars were frequently seen in the gray matter.

*6 krad.* Seven of the eight rats irradiated when 5 days old had neurologic changes at 11 to 12 days following irradiation; two of the seven died subsequent to the onset of these changes. The eighth animal died 17 days after irradiation but had remained normal neurologically during this period. Incontinence of urine was noted in some at the same time as the functional deficits of the hindlimbs were noted, but in others this visceral abnormality was not evident until as late as 9 days after onset of somatic changes. The surviving rats were killed 22 days following irradiation. The histologic appearances of the spinal cords were essentially the same as noted in the previous groups receiving 12 krad at a comparable age and can be summarized as follows: necrosis in center of irradiated area, cavities filled with gitter cells and debris primarily in white matter; destruction of axis cylinders, almost complete loss of myelin from the lesion with apparently well-myelinated white matter above and below; chromatolysis, large irregularly-shaped astrocytes, decrease in number of neuroglia in non-necrotic portions of irradiated area, hemorrhages and vascular dilatation in both gray and white matter; and vascular dilatation in the transitional zone between irradiated and non-irradiated areas.

Irradiation of eight rats 11 days old resulted in the development of neurologic abnormalities in 4 of these 23 to 24 days later. One animal died immediately after irradiation and three remained normal throughout the experimental period. The four rats with neurologic changes developed incontinence of urine within a week following the onset of disturbances in the hindlimbs and



Fig 3 Lo gitud nal section through lumba pi nal cord of rat irradiated with 12 krad when 4 d ys ld nd killed 23 day later Two large cysti reas cont in ng debris and gitter cells nd sur rounded by reactive cells these two adj cent necrot c reas lmost transect th pi al cord Cresyl echt violet sta n. 90



F g 4 Lumba region of spinal cord 5 day following dministration of 12 krad t this tructure in 9-day-old rat Th ventral wh t *matter is completely necroti d th necrot* area extends for sh rt distance t the gra matter throughout the section there is an increase in the n mber of cells. Hematox lin Gieson sta 90

All animals irradiated when 9 days old developed changes in the neurologic status of the hindlimbs at 15 days following irradiation Severe, concurrent alterations in bladder function made it impossible to extend the observation period beyond 23 days post irradiation The spinal cords from these animals were necrotic, with the greater extent of the necrosis in the white matter (Fig 4) Large cavities in the latter interrupted the continuity of axis cylinders (Fig 4) and only fragments of myelin were stained in such areas, whereas non irradiated regions appeared to be well myelinated Gitter cells were abundant in necrotic foci Neuronal degeneration was widespread but the cavities in the gray matter were not as numerous nor as large as were those in the white matter Hemorrhages were noted in both the gray and white matter and vascular dilatation and congestion were evident throughout the irradiated region and at the junction between this and the non irradiated areas Endothe-

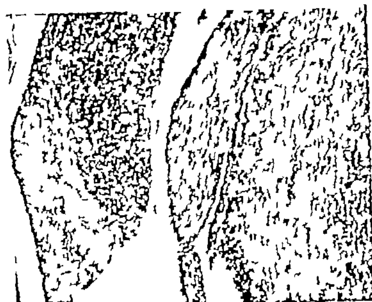


Fig. 6. Section showing nerve roots from rat irradiated with 6 krad when 14 days old and killed 65 days later. A portion of this root appears to be swollen and vacuolated and is highly cellular due to the presence of numerous phagocytic cells. Hematoxylin and eosin stain. × 100

noted particularly in the gray matter and was due to neuroglial proliferation. In the same area the astrocytic nuclei were hypertrophied and the nuclear membranes were quite prominent. Endothelial cells were hypertrophied and the vessels were slightly dilated. Some of the large motor neurons of the ventral horn region had an increased number of "satellite" cells (Fig. 5a); whether these cells were microglia or oligodendroglia is not certain at this time. There was no evidence of necrosis within the spinal cords, but small areas of degeneration were found in the spinal roots (Fig. 6). Other spinal cords from neurologically normal rats had changes similar to but of greater severity than those just described. The most severe changes were seen in only one spinal cord in which cavities were beginning to form in the white matter. Degeneration of myelin and presence of phagocytic cells were noted in the spinal roots of this animal also. This is the first group within which such variations in the type and the extent of the pathologic changes were noted at the same post-irradiation interval and in which histologic changes existed in the absence of neurologic abnormalities.

*3 krad.* All rats irradiated when 4 or 5 days old developed neurologic abnormalities 10 to 12 days later. One died soon after the onset of these abnormali-

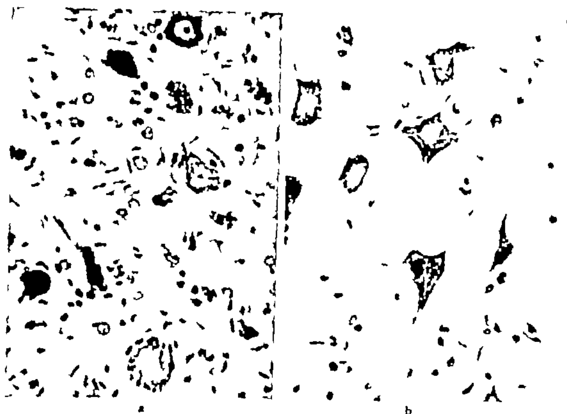



Fig 5. a) High-power view of gray matter in spinal cord of rat irradiated with 6 krad at 14 days of age and killed 63 day later The number of neuroglia is much greater than is seen in the control section (b) there is enlargement of some neuroglia and increase in the number of satellite cells of the neurons. b) High power view of gray matter from normal rat of the same age (77 days) as shown in ( ) Cresyl echt violet stain. × 650

had to be killed 39 days following irradiation The histologic changes within the spinal cords of these animals will not be repeated here because they are the same as those described for the comparable age group receiving 12 krad The rats that did not show any neurologic abnormalities were killed on day 70 following irradiation and no histologic changes were seen in their spinal cords.

Only one of the eight animals irradiated when 14 to 15 days of age had neurologic changes which became evident at 47 days after irradiation The other animals remained normal neurologically during the experimental period and all were killed 63 days following irradiation The microscopic alterations already described in previous groups were also seen in the spinal cord of the one rat with neurologic abnormalities of the hindlimbs In the other animals however histologic changes were seen in spite of the fact the rats appeared to be normal neurologically The mildest change was an increase in number of cells in the irradiated regions of the spinal cords (cf Fig 5) this increase was

1 700 rad/min, whereas the same amount was delivered at 635 to 892 rad/min in this experiment. Data pertaining to the relationship between dose rate and radiation-induced changes in the central nervous system are sparse (HICKS 1956, ZEMAN 1961) so that the influence, if any of this factor on the results presented by this investigation cannot be surmised. With a further decrease of the quantity of radiation to 3 krad it was found that this dose was effective in producing neurologic abnormalities in the youngest group only Whether or not neurological alterations would have occurred after the observation period of 63 or 70 days cannot be stated and it is unfortunate that circumstances did not permit this observation period to be extended several more months. The smallest doses of radiation in this experiment, i. e. 1.5 and 0.75 krad, did not produce any neurologic changes in any of the animals regardless of age at the time of irradiation. It could be concluded then that within the conditions and time limitations of this experiment the smallest amount of radiation which produced neurologic abnormalities in any age group was between 1.5 krad and 3 0 krad, and that the smallest amount effective in producing some degree of neurologic disturbance in all age groups was between 3 0 krad and 6 0 krad.

One aspect of the neurologic studies that deserves comment is the latent period, i. e. the time between irradiation and the onset of observable neurologic abnormalities. Among the older groups receiving 12 krad and 6.0 krad the length of the latent period was found to be related directly to the age at the time of irradiation, and inversely to the amount of radiation administered In contrast, the rats in the youngest group manifested these abnormalities at 9 to 12 days after irradiation regardless of the amonut of radiation administered (3 krad to 12 krad) Since this latent period was so constant and short, and since the youngest animals receiving 1.5 krad were still apparently normal as late as 69 and 70 days after irradiation, these data would indicate that 1.5 krad is incapable of producing neurological abnormalities, or that if such abnormalities did occur at a much later time they would probably be etiologically different from those seen at 9 to 12 days following irradiation. The constancy of the 9 to 12 day latent period was also noted in this investigator's earlier works (GILMORE 1963a, 1964)

The pattern of the incidence of neurologic abnormalities and of the latent periods in relation to age and amount of irradiation is similar to that reported by YAMAZAKI et coll (1960) following roentgen irradiation of the heads of rats 8 hours to 25 days of age. These investigators found that the greatest incidence of neurologic abnormalities occurred in animals irradiated during the first few days postnatally and that the incidence of these changes increased with the amount of radiation administered. The exception to this in the present study is

ties and the others were killed 18 days post irradiation. The same severe histologic alterations described in spinal cords of animals irradiated at a comparable age and killed 23 and 22 days following irradiation with 12 and 6 krad respectively were seen in these animals

All rats receiving 3 krad when 11 days of age remained normal neurologically throughout the 63-day experimental period No histologic changes were noted within the spinal cords of these animals but a small area of degeneration had developed in a spinal nerve root of one rat

A transient period of slight neurologic difficulty occurred in one of the eight rats irradiated when 14 days old this change, consisting of an inability to use the ankles properly was noted at 39 days following irradiation and persisted for about one week, after which the animal appeared to be normal. The remaining seven animals appeared to be normal throughout the experiment All rats were killed at 70 days following irradiation. The spinal cords were normal histologically with the exception of one which had slight changes consisting of swollen endothelium and proliferation of oligodendroglia and astroglia with nuclear hypertrophy in the latter There were no other changes in neurons, myelin axis cylinders or vascular system Spinal roots from several spinal cords however did have small areas of degeneration

*1 5 krad and 0 75 krad* Regardless of age at the time of irradiation all animals receiving 1 5 krad and 0 75 krad remained normal throughout the observation period All rats in these groups were killed 69 or 70 days following irradiation and no microscopic changes were noted in any of the spinal cords.

## Discussion

The data presented above indicate that the incidence of neurologic abnormalities resulting from irradiation of the neonatal nervous system is related to both age at the time of irradiation and to the amount of radiation administered

The effectiveness of 12 krad in inducing changes is evidenced by the occurrence of neurologic abnormalities in 50 % or more of the animals in all age groups When the total dose of radiation is decreased to 6 krad there is still a high incidence of neurologic changes in the two younger groups but a decreased incidence in the oldest group These data pertaining to the 6 krad group are different from those obtained in a previous study (GILMORE 1964) in which it was noted that the same amount of high energy protons produced a high incidence of neurologic abnormalities regardless of age at time of irradiation A comparison of experimental methods and conditions shows one difference to be in the dose rate In the earlier experiment the dose rate was *1 250 to*

experiment the neurologic and neuropathologic observations are related to the age at the time of irradiation and to the quantity of radiation administered. In addition to these observations the data have indicated that the dose rate is a factor to be considered in biologic experiments, but it is not likely that the dose-rate variation recorded during this experiment would alter the basic conclusions drawn in this paper. The data obtained from the groups receiving the smallest doses of radiation also stress the need for long-term studies in this area. Further investigation of these aspects as well as of the varying degrees of oxygenation in the individual animals, and perhaps also of the varying states of development in animals of the same extrauterine age, are needed for a more complete understanding of the response of the immature nervous system to ionizing radiation.

## Acknowledgements

Sincere appreciation is extended to Professor Bror Rexed and to Docent Börje Larsson whose aid, advice and efforts made this experiment possible, to the cyclotron crew for their efforts in providing the proton beam, and to Miss K. Hagman for preparation of the histologic material. The financial support was through USPHS Postdoctoral Research Fellowship BF 10, 691-C2 and the USAF School of Aerospace Medicine under Contract AF 61(052)-740 through the European Office of Aerospace Research (OAR) United States Air Force.

## SUMMARY

Single doses of high-energy protons ranging from 0.75 krad to 12 krad were administered to limited portions of spinal cords of neonatal rats when 3 to 5, 9 to 11, or 14 to 16 days of age. The incidence of neurologic abnormalities in the hindlimbs and the time between irradiation and onset of these abnormalities were studied and are discussed with respect to age when irradiated and amount of radiation. The microscopically pathologic changes of the spinal cords are reported and discussed in relation to age, dose and the neurologic status of the animal.

## ZUSAMMENFASSUNG

Einzeldosen von hochenergetischen Protonen von 0.75 bis 12 krad wurden umschriebenen Gebieten des Rückenmarks neugeborener Ratten im Alter von 3 bis 5, 9 bis 11, 14 bis 16 Tagen verabreicht. Das Auftreten von neurologischen Veränderungen der hinteren Extremitäten sowie das Zeitintervall zwischen Bestrahlung und dem Auftreten dieser Schädigungen wurde studiert und mit Hinsicht auf das Alter und die Strahlendosis diskutiert. Es werden die mikroskopischen Befunde des Rückenmarks mitgeteilt und mit Hinsicht auf Alter, Dosierung und den neurologischen Status des Versuchstieres besprochen.

that almost all of the youngest rats receiving 3 krad to 12 krad developed neurologic changes and that the difference in amounts of radiation did not alter this incidence YAMAZAKI et coll (1960) also noted that the latent period increased with increasing age and decreasing dose In the present investigation the exception to this pattern is the youngest group for which the latent was 9 to 12 days regardless of the amount of radiation administered

The studies of the microscopic changes found histologically in the spinal cords from most rats receiving 12 krad and from the 3 to 5 day and 9 to 11 day groups receiving 6 krad indicated that these amounts of radiation can produce very severe damage in the central nervous system The data also indicated that these changes developed very rapidly since the studies were made on spinal cords from animals that had been killed at about 5 weeks or less following irradiation Whether or not the remaining rats receiving 6 krad at 9 to 11 and 14 to 15 days of age would have developed severe histologic changes with subsequent neurologic abnormalities is still open to question In some of these it was interesting to note that there was an increased number of neuroglia throughout the irradiated areas or in some cases, an increase in satellite cells. In addition cavities were beginning to form in the white matter and degenerative changes in the spinal roots were seen in one animal On the basis of these histologic changes one might hypothesize that neurologic abnormalities could have developed in a few more rats if the length of the experimental period had been extended

In contrast to the higher doses of radiation 3 krad was effective in producing severe pathologic changes in only the youngest group Only one spinal cord from rats given this amount when 9 to 11 or 14 to 16 days of age had histologic alterations and this was from the rat that had had a period of transient paralysis All other spinal cords were normal with the exception of several in which small areas of degeneration were beginning to form in the spinal nerve roots Since some pathologic changes were becoming evident in the spinal roots one might hypothesize again that an extension of the experimental period would have given different results in terms of incidence of neurologic abnormalities and of latent periods

The long term effects of 1 5 krad and 0 75 krad would be of interest in view of the changes that are known to occur in the central nervous system of adult rats at considerably long intervals following irradiation (ZEMAN 1961 INNES & CARSTEN 1961a 1961b) In addition a study of neurologic abnormalities and histologic changes resulting from amounts of radiation between 1 5 krad and 3 krad would be of interest in determining why such different results occur when these amounts of radiation are administered to 3 to 5 day old rats.

This study has shown that within the dose age and time limits of this

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# PLACENTAL TRANSFER OF STRONTIUM 85 IN MICE

by

ARNE NELSON, CURT RÖNNBÄCK and ANN MARIE SJÖDÉN

The high radiosensitivity of the foetus has made the placental transfer of radiostrontium of particular interest. A number of investigations have been performed. The transfer of $^{89}Sr$ from mother to foetus has been investigated in our laboratories and reported by HOLMBERG, NELSON & WALLGREN (1960). The investigation included the time-course of uptake by the end of gestation, the uptake at different stages of gestation, and the foetal uptake in matings at different time-intervals following injection of the females. The results disclosed that the ability of the foetal skeleton to take up $^{89}Sr$ appeared after the 14th day of gestation, and it was further demonstrated that $^{89}Sr$ injected into the mother was available to the foetus in undiminished quantity for at least 4 weeks.

The accessibility of $^{85}Sr$ which is a $\gamma$-emitter and of a small-animal counter with plastic scintillator have made it possible for us to repeat the investigation with greater accuracy and to obtain supplementary data.

*Material and Methods.* A total number of 560 pregnant CBA female mice all approximately 75 days old at the start of the experiment, were used.

Submitted for publication 28 January 1965.

## RÉSUMÉ

Des doses uniques de protons de haute énergie, comprises entre 0 75 krad et 12 krad ont été administrées à des portions limitées de la moelle épinière de rats nouveau-nés âgés de 3 à 5 9 à 11 ou 14 à 16 jours. L auteur a étudié la fréquence et le délai d apparition de troubles neurologiques des membres postérieurs en fonction de l âge au moment de l irradiation et de la quantité de rayonnement. Il décrit les lésions histologiques de la moelle épinière et les étudie en fonction de l âge, de la dose et des signes neurologiques.

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**Table 2**

*A — Results of series I*

| Day of pregnancy | Time between inj. and sacrifice | Mean litter size | Initial measurement, cpm in thousands (mean ± SE) | Measurement at sacrifice, cpm in thousands (mean ± SE) | Activity of foetus cpm in thousands (mean ± SE) | Activity of foetus in % of that of pregnant mother* |
|---|---|---|---|---|---|---|
| 12 | 15 min | 7.67 | 54.03 ± 1.41 | 52.80 ± 1.35 | 0.02 ± 0.01 | 0.03 ± 0.01 |
| | 45 | 6.87 | 51.11 ± 1.94 | 51.55 ± 1.98 | 0.03 ± 0.01 | 0.05 ± 0.01 |
| | 90 | 7.80 | 53.56 ± 2.10 | 49.18 ± 1.62 | 0.03 ± 0.01 | 0.05 ± 0.01 |
| | 180 | 7.13 | 53.35 ± 2.06 | 51.93 ± 1.26 | 0.02 ± 0.01 | 0.04 ± 0.01 |
| | 240 | 5.73 | 50.29 ± 2.15 | 44.26 ± 2.71 | 0.02 ± 0.01 | 0.05 ± 0.01 |
| 14 | 15 min | 6.93 | 59.33 ± 1.84 | 57.82 ± 2.17 | 0.06 ± 0.01 | 0.10 ± 0.02 |
| | 45 | 7.67 | 62.59 ± 1.99 | 56.08 ± 1.87 | 0.10 ± 0.02 | 0.18 ± 0.03 |
| | 90 | 7.00 | 58.29 ± 1.50 | 52.28 ± 2.08 | 0.09 ± 0.02 | 0.18 ± 0.03 |
| | 180 | 7.20 | 55.12 ± 2.52 | 48.03 ± 1.82 | 0.08 ± 0.01 | 0.17 ± 0.03 |
| | 240 | 7.06 | 52.92 ± 2.11 | 48.23 ± 2.23 | 0.06 ± 0.01 | 0.14 ± 0.02 |
| 16 | 15 min | 6.95 | 61.12 ± 2.82 | 58.61 ± 2.40 | 0.18 ± 0.01 | 0.31 ± 0.02 |
| | 45 | 7.00 | 53.28 ± 1.76 | 53.30 ± 1.72 | 0.26 ± 0.02 | 0.49 ± 0.04 |
| | 90 | 7.13 | 59.51 ± 2.53 | 53.50 ± 2.28 | 0.37 ± 0.01 | 0.71 ± 0.04 |
| | 180 | 6.80 | 58.29 ± 2.62 | 53.48 ± 2.89 | 0.43 ± 0.03 | 0.81 ± 0.01 |
| | 240 | 6.87 | 60.55 ± 1.99 | 53.76 ± 2.49 | 0.51 ± 0.02 | 0.98 ± 0.01 |
| 18 | 15 min | 7.20 | 55.71 ± 1.33 | 56.49 ± 1.38 | 0.58 ± 0.04 | 1.03 ± 0.06 |
| | 45 | 7.73 | 55.51 ± 1.12 | 53.82 ± 1.51 | 0.96 ± 0.05 | 1.81 ± 0.11 |
| | 90 | 7.66 | 55.89 ± 0.78 | 52.07 ± 1.40 | 1.21 ± 0.05 | 2.33 ± 0.09 |
| | 180 | 6.64 | 54.33 ± 1.52 | 52.33 ± 1.74 | 1.45 ± 0.05 | 2.80 ± 0.11 |
| | 240 | 6.47 | 58.81 ± 1.43 | 55.92 ± 3.50 | 1.61 ± 0.08 | 2.92 ± 0.14 |
| | | | *B — Results of series II* | | | |
| 12 | 90 min | 5.70 | 53.14 ± 3.11 | 49.37 ± 2.76 | 0.05 ± 0.01 | 0.10 ± 0.02 |
| | 2 days | 7.07 | 54.82 ± 2.47 | 24.23 ± 0.94 | 0.04 ± 0.01 | 0.15 ± 0.03 |
| | 4 | 4.81 | 70.24 ± 2.97 | 30.33 ± 1.42 | 0.04 ± 0.04 | 0.15 ± 0.04 |
| | 6 | 7.56 | 62.78 ± 2.96 | 22.42 ± 1.38 | 0.15 ± 0.01 | 0.68 ± 0.05 |
| 14 | 90 min | 7.30 | 81.09 ± 2.46 | 57.40 ± 3.20 | 0.16 ± 0.02 | 0.27 ± 0.03 |
| | 2 | 7.07 | 69.80 ± 2.24 | 32.64 ± 1.75 | 0.13 ± 0.02 | 0.42 ± 0.07 |
| | 4 | 7.21 | 73.48 ± 1.71 | 32.18 ± 1.55 | 0.29 ± 0.01 | 0.90 ± 0.06 |
| 16 | 90 min | 7.00 | 61.31 ± 3.77 | 57.72 ± 3.80 | 0.50 ± 0.04 | 0.87 ± 0.05 |
| | 2 days | 7.23 | 67.50 ± 3.44 | 34.87 ± 1.39 | 1.46 ± 0.10 | 4.21 ± 0.28 |
| 18 | 80 min | 7.90 | 75.87 ± 3.39 | 78.81 ± 2.81 | 1.42 ± 0.06 | 1.82 ± 0.08 |
| | | | *C — Results of series III* | | | |
| | 1 week | 7.85 | 71.30 ± 0.81 | 18.67 ± 0.82 | 0.10 ± 0.01 | 0.53 ± 0.08 |
| | 2 weeks | 7.23 | 81.93 ± 4.77 | 20.42 ± 0.79 | 0.10 ± 0.02 | 0.47 ± 0.07 |
| | 4 | 6.74 | 77.78 ± 1.43 | 13.81 ± 0.96 | 0.03 ± 0.02 | 0.42 ± 0.06 |

Activity of foetuses = mean activity (and SE) of the mean foetus of each litter

*The mean of the mean activity of the foetuses in each litter in percent of the activity of its pregnant mother

Table 1

*Experimental scheme*

| *Number of litters at different time-intervals between injection and sacrifice* | Day of pregnancy | | | | | | |
|---|---|---|---|---|---|---|---|
| | | 15 | 45 | 90 | 180 | 240 | min |
| Series I | 12 | 15 | 15 | 15 | 15 | 15 | 15 |
| | 14 | 15 | 15 | 15 | 15 | 15 | 15 |
| | 16 | 15 | 15 | 15 | 15 | 15 | 15 |
| | 18 | 15 | 15 | 15 | 15 | 15 | 15 |
| | | 90 min | 2 days | 4 days | 6 days | 8 days | 10 days |
| Series II | 12 | 10 | 15 | 15 | 15 | — | 15 |
| | 14 | 10 | 15 | 15 | — | 15 | — |
| | 16 | 10 | 15 | — | 15 | — | — |
| | 18 | 10 | — | 15 | — | — | — |
| *Number of litter from females injected at different time-intervals before mating* | | 1 week | | 2 weeks | | | 4 weeks |
| Series III | 18 | 20 | | 20 | | | 20 |

The radiostrontium used consisted of $^{85}$Sr nitrate in nitric acid solution diluted with physiologic saline The injection volume was in all cases 0.3 ml and contained about 0 3 $\mu$Ci of $^{85}$Sr This activity gave a counting rate of approx 59 000 cpm at the initial measurement in the animal injected

The animals were mated and the day of pregnancy was determined by controlling the vaginal plug The females were injected in a tail vein on different days of pregnancy (the 12th 14th 16th and 18th) with $^{85}$Sr solution and were measured within three minutes in the small-animal counter (NILSSON 1961) This counter consists of a large well-shaped plastic crystal detector having a length of 240 mm and a diameter of 90 mm attached to the scintillator is a photomultiplicator tube connected to a conventional counter unit. The animals were put in a cylindric plastic box and placed in the detector in such a way that the center was on the central axis of the crystal After a certain time the activity of the females was measured again and then they were sacrificed the weight and activity of each foetus was determined.

The experiment was carried out in three stages as indicated in Table 1



Fig. 2. Rate of uptake of strontium 85 (90 min to 6 days) administered t various days of gestation.

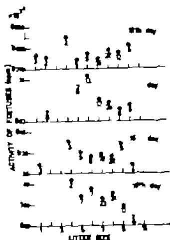


Fig. 3. Relation between mean foetal activity and litter size; figures t the points indicate number of litters.

values representing changes with time do not deviate from the well-known strontium excretion curve in non pregnant animals.

The activity of the foetuses recorded in Table 2 is the mean of the mean foetal activity within each litter A decrease in activity per foetus with increasing litter size could have been expected but such a tendency was not observed (see Fig 3) this confirms results obtained by NEUMANN & KRIEGEL (1961) The apparent effect at the 18th day of examination is due to two extreme values. However only two litters in each group were observed hence the great distribution.

The values recorded in the last column of Table 2 activity of foetus in / of that of the pregnant mother' are the means of the mean activity of the foetuses in each litter as a percentage of the activity of the pregnant mother After administration of radiostrontium on the 12th day of gestation, a very low and constant percentage was observed up to and including the 16th day On the 18th day however it increased 4 to 6 times. Administration on the 14th day produced similar results even if the percentage was a little higher from the beginning also in this case there was an increase on the 18th day Injection on the 16th day increased the percentage of activity already for the short time-intervals, and a very high increase was noted on the 18th day

Administration of the radiostrontium on the 18th day produced a very different picture. The uptake was high from the beginning and the curve made a steep slope up to 180 min, at which point it seemed to become level

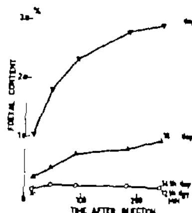



Fig 1 Rate of uptake of Sr (15 to 240 min) administered at various days of gestation.

## Results

The results of the investigation are shown in Table 2 and Figs 1 and 2 The short time intervals (Table 2 A) were chosen in order to give an idea of the time-course of the foetal uptake of strontium on different days of gestation i e the distribution rate after administration

*Equilibrium* seems to occur very early on the 12th 14th and 16th day of gestation but on the 18th day it takes a little longer At 240 min after the administration however the slope appears to be levelled Because of the difficulties in isolating embryos macroscopically before the 12th day no measurements were made earlier and due to the 2-day intervals between examinations the 18th day has been the last one. On the 20th and sometimes on the 19th day the mice begin to bring forth young

The longer time-intervals (Table 2 B) *indicate the transfer of* $^{90}$*Sr from* mother to foetus due to the growth of the foetuses and their ossification

The administration of strontium before mating was undertaken *in order to* investigate the effect of gestation on the strontium incorporated in the skeleton of the mother

It may be noted that the results of the initial measurements are relatively constant The observed distribution is in part due to *the difficulties in achieving* constant geometry since the mice were not anaesthetized and in part to the method of measurement The same applies to the results of measurements at *sacrifice*

The differences between the initial measurements and the measurements at *sacrifice are insignificant* for the short time-intervals in series I The excretion from the mothers seems to be too small In series II and III the differences are obvious, the greatest being *evident between measurements* at 90 min and at 2 days After this time the differences seem to be fairly *consistent* The

## Acknowledgement

The authors wish to express their thanks to Mr Ola Hertzberg and Miss Elisabeth Engström for the statistical treatment and to Miss Sonja Falk for technical assistance.

## SUMMARY

The placental transfer of $^{85}Sr$ in mice has been examined. If the strontium is administered before mating the foetal uptake is low. The rate of uptake by the foetuses after foetuses injection on the 12th, 14th or 16th day of gestation is dependent on the growth of the foetus, i.e. the size. The high uptake on the 18th day is due to the ossification of the foetal skeleton.

## ZUSAMMENFASSUNG

Die Übertragung von $^{85}Sr$ durch die Placenta von Mäusen wurde erforscht. Die Aufnahme des Strontiums durch den Fötus ist gering wenn das Strontium vor der Copulation eingereicht wird. Wenn man das Strontium am 12ten, 14ten oder 16ten Tag der Schwangerschaft einspritzt, hängt die Aufnahme des Strontiums in den Fötus von dessen Entwicklungsstadium ab. Die am 18ten Tage beobachteten hohen Aufnahme hängt mit der Knochenentwicklung zusammen.

## RÉSUMÉ

Les auteurs ont étudié la traversée placentaire de $^{85}Sr$ chez les souris. Si le strontium est administré avant l'accouplement, la fixation foetale est faible. Le taux de fixation par les foetus après injection aux 12e, 14e ou 16e jour de la gestation dépend de la croissance du foetus, c'est-à-dire de sa taille. La forte fixation au 18e jour est due à l'ossification du squelette foetal.

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When radiostrontium was administered before mating the uptake on the 18th day of gestation was 0.4 to 0.5 % with no significant difference between 1 and 4 weeks.

## Comments

The placental transfer during the second half of gestation is dependent on at which day of gestation the radiostrontium has been administered. It was found when the foetal content was determined 90 min after injection, that the mean foetal weight on the 12th day of gestation was ~ 0.03 g with an uptake of radiostrontium from the mother of only 0.05 to 0.10 % on the 14th day the weight was ~ 0.10 g and the uptake 0.2 to 0.3 % on the 16th day the weight was 0.3 g and the uptake 0.7 to 0.9 % and on the 18th day the values were 0.7 g and 1.8 to 2.3 % respectively.

These results confirm the findings of KRIEGEL (1960) in rats, and of STERNBERG (1960) in guinea pigs. These authors reported a linear correlation between the weight of the embryos and the strontium content, but according to KRIEGEL it was valid only for the development during the last 3 to 4 days of gestation. Our results however indicate a correlation between the weight and the short term uptake during the whole second half of the gestation period. In those cases in which strontium was administered on the 12th on the 14th and on the 16th day of gestation and the activity measured on the 18th day the foetal uptake was observed to be much greater on the 18th day than on previous days. This observation corresponds with the results obtained by HOLMBERG et coll (1960). The small discrepancies noted are probably due to different methods of measurement and to the fact that different gestation days were used in the two investigations.

The significant increase in the foetal uptake on the 18th day is obviously due to ossification of the foetal skeleton which seems to start on the 15th day (ZORZOLI 1948 HOLMBERG et coll 1960). KOLLMER & KRIEGEL (1963) assumed that the initial incorporation of strontium into the females skeleton was finished before the third day after injection the amount of strontium in the blood being less than 0.001 % of the dose injected. This observation has been confirmed by the present authors in an investigation (unpublished) which showed that no 'Sr could be measured in the blood after 48 hours. Thus the radiostrontium taken up by the foetuses derives mainly from the maternal skeleton and the rate of placental transfer does not seem to exceed the needs of the growing embryo (STERNBERG 1960). If radiostrontium is administered a relatively short time before mating the foetal uptake by the 18th day of gestation is low and the radiostrontium originates from the maternal skeleton.

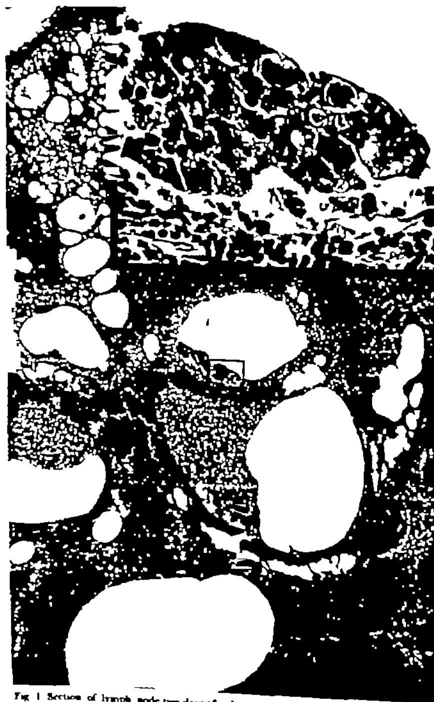



Fig 1 Section of lymph node two days after lymphography. A clump of carcinoma cells [illegible] lies free in [illegible] sinus distended by oily contrast medium.

FROM THE DEPARTMENT OF GYNAECOLOGY, RADIUMHEMMET, THE DEPARTMENT OF SURGERY, SERAFIMERLASARETTET, THE CYTOLOGY DEPARTMENT OF RADIUMHEMMET AND THE INSTITUTE OF RADIOPATHOLOGY, STOCKHOLM, SWEDEN

# THORACIC DUCT CANNULATION IN LYMPHOGRAPHY IN MAN

## Preliminary report

by

BENGT TJERNBERG, BENGT WERNER and JOSEF ZAJICEK

There is as yet no suitable alternative to oily contrast media for lymphographic examination of lymph vessels and nodes in the retroperitoneal region and the posterior mediastinum. The intralymphatic injection of these media is associated with certain risks, such as oil embolism, chiefly to the lungs, and lipogranuloma in lymph nodes (for reference see TJERNBERG 1962 and RÜTTIMANN & DEL BUONO 1964). A question of the utmost practical importance is whether or not the contrast medium during its passage through a *malignantly* altered lymph node can release and transport malignant cells or cell plugs, thereby promoting spread of the tumour. That this hazard cannot be disregarded is illustrated in Fig. 1, in which a lymph node with metastases from a malignant embryonal testicular tumour is shown; a clump of tumour cells lies free in a sinus greatly distended by the oily contrast medium, Lipiodol Ultra Fluide* (André Guerbet et Cie).

Submitted for publication 26 January 1965



Fig. 1 Section of lymph node two days after lymphography. A clump of carcinoma cells (inset) lies free in ... sinus distended by oily contrast medium.

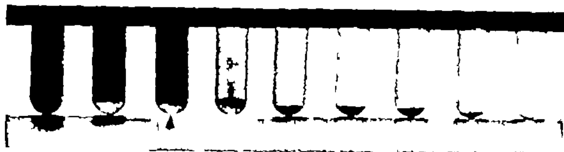


Fig 2 Consecutive samples of thoracic duct lymph collected during lymphography The contrast medium formed sediment in the tubes I gradually diminishing amounts, beginning in the second tube from the left no sediment is evident in the first and last tubes of the series.

A series of investigations in patients with malignant tumours was started in an attempt to elucidate pertinent aspects of the problem The initial aims were (1) to determine how much of an oily contrast medium injected into the lymphatics of the foot passes via the thoracic duct into the venous system in the neck in direct association with the injection and (2) to observe if the medium transports tumour cells from the lymph nodes through which it passes

Lymph was collected by means of a plastic catheter introduced into the cervical part of the thoracic duct just before the duct enters the venous system (cf CARLSTEN & HAMBERGER 1957) according to the method described by BLOMSTRAND FRANKSSON & WERNER (1965) Heparinized glass tubes were used to collect the lymph samples.

The thoracic duct having thus been cannulated lymphography was performed by the injection of Lipiodol UF via polythene catheters into the lymphatics of a foot with the aid of a motor-driven apparatus (TJERNBERG 1962) The lymph sampled during and after injection of the contrast medium was analyzed for its content of Lipiodol This was done by allowing the samples to stand in the glass tubes, when the greater specific weight of the Lipiodol (1 23) as compared with that of thoracic duct lymph (1 015 to 1 025) caused the former to settle The lymph above the oily sediment was pipetted off for cytologic examination by the technique described by TJERNBERG & ZAJICEK (1964) The Lipiodol in the bottom of the tubes was washed with 0 9 % NaCl and the washings were added to the previously separated lymph for cytologic analysis. The volume of medium was then determined

An illustrative case is that of a 37 year-old man whose left testis had been removed because of adenocarcinoma A total of 8 5 ml Lipiodol UF was injected into a lymphatic of the dorsum of the left foot at a rate of 0 08 ml/minute Samples of the thoracic duct lymph and sediments of contrast medium collect

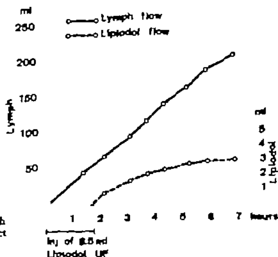



Fig. 3 Same case as in fig. 2. Flow of lymph and contrast medium in the thoracic duct after injection of 8.5 ml Lipiodol into lymphatic of the foot.

ed during the experiment are shown in Fig 2 Drops of contrast medium began to appear in the collected lymph 1 hr and 40 min after the commencement of the infusion which was then promptly stopped. The contrast medium continued to appear in the lymph samples for no less than 5 hours however The total recovery of the medium during the experiment was 3 1 ml. The course of the lymph and contrast medium collection is presented graphically in Fig 3 Roentgenograms demonstrated contrast filling of lymph vessels and nodes all the way from the left foot up to the site of the catheter in the thoracic duct in the neck

A small portion of the unrecovered 5 4 ml of injected contrast medium may have passed to the venous system via possible lymphovenous anastomoses, but the major portion probably remained in the lymph nodes. No pulmonary oil embolism was detected roentgenologically

The results of the experiments up to the present time indicate that cannulation of the thoracic duct following injection of a substance into lymphatics of the lower extremity permits recovery of that portion which after transportation through the lymphatic system in the pelvis and along the spine, would otherwise have passed into the venous system via the thoracic duct. This possibility may be useful in research. It may also have practical uses, for example when it is desirable for some reason to prevent as far as possible passage to the circulating blood of substances injected into lymphatics for diagnostic or therapeutic purposes.

Further details of the investigations will be published later

## SUMMARY

Cannulation of the thoracic duct in the neck was performed in connection with lymphography of the lymphatic system of the pelvis and along the spine in a patient operated upon for carcinoma of the testis. The lymph collected was examined for the presence of tumour cells and contrast medium.

## ZUSAMMENFASSUNG

In einem Patienten der fur Testis-Karzinom operiert war wurde wahrend Lymphographie des Lymphsystemes des Beckens und der Lymphgefasse entlang der Wirbelsaule eine Kanüle in den Ductus thoracicus eingeführt. Die abgesaugte Lymphe wurde auf Tumor zellen und Kontrastmittel untersucht.

## RÉSUMÉ

*Le canal thoracique d un malade opéré pour cancer du testicule a été cathétérisé au cou à* l occasion d une lymphographie du système lymphatique pelvien et le long de la colonne vertébrale La lymphe recueillie a été examinée pour rechercher des cellules tumorales et le moyen de contraste.


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## SUMMARY

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